EXHIBIT “A”

Carcinogenicity of drinking coffee, mate, and very hot beverages

In May, 2016, a Working Group of 23 scientists from ten countries met at the International Agency for Research on Cancer (IARC) in Lyon, France, to evaluate the carcinogenicity of drinking coffee, mate, and very hot beverages. These assessments will be published in volume 116 of the IARC Monographs.[1]

Coffee is one of the world's most widely consumed beverages. It contains many different compounds and its composition varies depending on how it is produced and prepared for drinking. After consumption, caffeine, chlorogenic acids, and other compounds contained in coffee are absorbed and distributed throughout the body.

The carcinogenicity of coffee drinking was last assessed by IARC in 1991.[2] At that time coffee was classified as "possibly carcinogenic to humans" (Group 2B) based on limited evidence of an association with cancer of the urinary bladder from case-control studies, and inadequate evidence of carcinogenicity in experimental animals. However, there was also evidence suggesting a lack of carcinogenicity for cancers of the female breast and the large intestine.

For this re-evaluation, a much larger database of more than 1000 observational and experimental studies was available. In assessing the accumulated epidemiological evidence, the current Working Group gave the greatest weight to well-conducted prospective cohort and population-based case-control studies that controlled adequately for important potential confounders, including tobacco and alcohol consumption. For bladder cancer, there was no consistent evidence of an association with drinking coffee, or of an exposure–response gradient from ten cohort studies and several population-based case-control studies in Europe, the USA, and Japan.[3–5] In several studies, relative risks were increased in men but were null or decreased in women, consistent with residual confounding from smoking or occupational exposures among men. The Working Group concluded that positive associations reported in some studies could have been due to inadequate control for tobacco smoking, which can be strongly associated with heavy coffee drinking. By contrast, for endometrial cancer, the five largest cohort studies showed mostly inverse associations with coffee drinking. These results were supported by the findings of several case-control studies and a meta-analysis.[6] Inverse associations with coffee drinking were also observed in cohort and case-control studies of liver cancer in Asia, Europe, and North America. A meta-analysis of prospective cohort studies estimated that the risk of liver cancer decreases 15% for each 1 cup per day increment.[7] More than 40 cohort and case-control studies and a meta-analysis[8] including nearly 1 million women consistently indicated either no association or a modest inverse association for cancer of the female breast and coffee drinking. Similarly, numerous cohort and case-control studies of cancers of the pancreas and prostate consistently indicated no association between these cancers and coffee drinking. Data were also available for more than 20 other cancers, including lung, colorectal, stomach, oesophageal, oral cavity, ovarian, and brain cancers, and childhood leukaemia. Although the volume of data for some of these cancers was substantial, the Working Group judged the evidence to be inadequate for all of the other cancers reviewed for reasons including inconsistency of findings across studies, inadequate control for potential confounding, potential for measurement error, selection bias or recall bias, or insufficient numbers of studies.

The combination of evidence suggesting lack of carcinogenicity for cancers of the female breast, pancreas, prostate, uterine endometrium, and liver, with inverse associations for the latter two and inadequate evidence for all the other sites reviewed led to the conclusion that there is inadequate evidence in humans for the carcinogenicity of coffee drinking.

Coffee has been evaluated for carcinogenicity in several long-term studies in mice and rats, and has been tested for both tumour-promoting and cancer-preventing activity in a number of co-carcinogenicity studies in rats and hamsters. The Working Group concluded that these studies provided inadequate evidence in experimental animals for the carcinogenicity of coffee.

Coffee drinking exhibited strong antioxidant effects in studies in humans, including in randomised controlled trials.[9] Results for genotoxicity from studies in humans were inconsistent, and coffee did not induce chromosomal damage in rodents. Nonetheless, coffee gave positive results in bacterial mutagenesis assays, but only without metabolic activation. Coffee promoted apoptosis in human cancer cell lines.[10] Moderate evidence of an association of coffee drinking with reduced risk of colorectal adenoma was noted. Coffee has also been associated with beneficial effects on liver fibrosis and cirrhosis.

Overall coffee drinking was evaluated as unclassifiable as to its carcinogenicity to humans (Group 3).

Mate is an infusion made from dried leaves of *Ilex paraguariensis*. It is consumed mainly in South America and to a lesser extent in the Middle East, Europe, and North America. Mate is traditionally drunk very hot (>65°C), but it can also be consumed warm or cold. The carcinogenicity of mate was previously evaluated in 1991,[2] when

Published **Online**
June 15, 2016
http://dx.doi.org/10.1016/S1470-2045(16)30239-X

For more on the **IARC Monographs** see http://monographs.iarc.fr

Upcoming meetings
October 4–11, 2016, Volume 117: Pentachlorophenol and some related compounds;
March 21–28, 2017, Volume 118: Welding, welding fumes and some related chemicals

IARC Monograph Working Group Members
L T Stayner (USA)—meeting chair; E Milne (Australia); S Knasmüller (Austria); A Farah, L F Ribeiro Pinto (Brazil); D W Lachenmeier (Germany); C Bamia (Greece); A Tavani (Italy); M Inoue (Japan); N Djordjevic (Serbia); P C H Hollman, P A van den Brandt (Netherlands); J A Baron, E Gonzalez de Mejia, F Islami (unable to attend); C W Jameson, F Kamangar, D L McCormick, I Pogribny, I I Rusyn, R Sinha, M C Stern, K M Wilson (USA)

Declaration of interests
MI is the beneficiary of a financial contribution from AXA Research fund as chair holder of the AXA Department of Health and Human Security, Graduate School of Medicine, The University of Tokyo from Nov 1, 2012. AXA Research has no role in this work. All other working group members declare no competing interests.

Invited Specialists
None

Representatives
A Morise, for the French Agency for Food, Environmental and Occupational Health and Safety (ANSES), France

Declaration of interests
All representatives declare no competing interests.

Observers
V Guercio, for the Mario Negri Institute of Pharmacological Research, Italy; T Hatzold, for the Institute for Scientific Organization on Coffee (ISIC), Switzerland; A Leviton, for the National Coffee Association, USA; F Phillips, Freelance Dietitian and Nutrition Consultant, UK; V Thomas, for the University Paris Dauphine, France; C Wallmann, for the University of Kent, UK; M Wilde, for the University of Kent, UK

Declaration of interests
TH was an employee of Modelez International until November, 2015, holds stock options for Modelez International, and is a consultant to the Institute for Scientific Information on coffee. AL represents the National Coffee Association of the USA. All other observers declare no competing interests.

IARC/WHO Secretariat
B Abedi-Ardekani; L Benbrahim-Tallaa; V Bouvard; F El Ghissassi; Y Grosse; N Guha; K Z Guyton; I Huybrechts; B Lauby-Secretan; D Loomis; H Mattock; H Noh; S Pisanu; J Rothwell; A Scalbert; K Straif; M Zhivagui

Declaration of interests
All secretariat declare no competing interests.

For the **Preamble to the IARC Monographs** see http://monographs.iarc.fr/ENG/Preamble/index.php

For **IARC declarations of interests** see http://monographs.iarc.fr/ENG/Meetings/vol116-participants.pdf

hot mate drinking was classified as "probably carcinogenic to humans" (Group 2A).

Evidence on the carcinogenicity of mate comes mainly from hospital-based case-control studies on cancer of the oesophagus in South America. A pooled analysis[11] of most of the available studies showed the risk of oesophageal cancer increasing with the quantity of mate consumed. However, the trend was statistically significant only for mate consumed "hot" or "very hot", and a significant trend was observed with drinking temperature independent of the amount consumed. The single study that examined cold mate drinking showed no association with oesophageal cancer.

To further assess the effect of beverage temperature, the Working Group reviewed studies that reported on the association of oesophageal cancer with the drinking temperature of other beverages. Another pooled analysis[12] of South American case-control studies on oesophageal cancer showed significantly increased relative risks for drinking very hot tea and very hot beverages other than mate similar in magnitude to that for drinking very hot mate. A large cohort study and several case-control studies[13] showed an increased risk of oesophageal cancer when drinking tea very hot or hot, compared with lower temperatures. Similar results have been reported in other studies evaluating combinations of very hot drinks.

From these data, the Working Group concluded that there is limited evidence in humans for the carcinogenicity of drinking very hot beverages, and inadequate evidence in humans for the carcinogenicity of drinking mate that is not very hot.

In experimental animals, the carcinogenicity of mate and of beverage temperature has only been assessed in a few co-carcinogenicity studies. Locally instilled very hot water (at 65–70°C) increased the incidence of nitrosamine-induced oesophageal tumours in one study in mice[14] and one study in rats.[15] By contrast, cold mate administered as drinking fluid in rats reduced the incidence of oesophageal and liver tumours induced by nitrosamine and hot water combined. The Working Group concluded that there is limited evidence in experimental animals for the carcinogenicity of very hot water at 65°C or above, and inadequate evidence in experimental animals for the carcinogenicity of mate as a drinking fluid.

Pharmacokinetic and mechanistic data for mate drinking are sparse. Studies in humans and animals given orally administered mate did not report genotoxicity or other cancer related effects.

The Working Group noted that the epidemiological evidence for very hot beverages and human cancer has strengthened over time, with positive associations and trends in studies that considered qualitative gradations of temperature. Additionally, new studies in experimental animals show that hot water above 65°C can act as a tumour promoter. Although the mechanistic and other relevant evidence for very hot beverages is scant, biological plausibility exists for an association between very hot beverages and cell injury and the sequelae that might lead to cancer. On the basis of these considerations and on the totality of the evidence, drinking very hot beverages at above 65°C was classified as "probably carcinogenic to humans" (Group 2A). This evaluation of very hot beverages includes drinking of very hot mate. Drinking mate that is not very hot was evaluated as "not classifiable as to its carcinogenicity to humans" (Group 3).

We declare no competing interests.

Dana Loomis, Kathryn Z Guyton, Yann Grosse, Béatrice Lauby-Secretan, Fatiha El Ghissassi, Véronique Bouvard, Lamia Benbrahim-Tallaa, Neela Guha, Heidi Mattock, Kurt Straif, on behalf of the International Agency for Research on Cancer Monograph Working Group

International Agency for Research on Cancer, Lyon, France

1 International Agency for Research on Cancer. Volume 116: coffee, mate and very hot beverages. IARC Working Group. Lyon, France; 24–31 May, 2016. *IARC Monogr Eval Carcinog Risks Hum* (in press).
2 International Agency for Research on Cancer. Coffee, tea, mate, methylxanthines and methylglyoxal. *IARC Monogr Eval Carcinog Risks Hum* 1991; **51:** 1–513.
3 Zeegers MP, Dorant E, Goldbohm RA, van den Brandt PA. Are coffee, tea, and total fluid consumption associated with bladder cancer risk? Results from the Netherlands Cohort Study. *Cancer Causes Control* 2001; **12:** 231–38.
4 Michaud DS, Spiegelman D, Clinton SK, et al. Fluid intake and the risk of bladder cancer in men. *N Engl J Med* 1999; **340:** 1390–97.
5 Nagano J, Kono S, Preston DL, et al. Bladder-cancer incidence in relation to vegetable and fruit consumption: a prospective study of atomic-bomb survivors. *Int J Cancer* 2000; **86:** 132–38.
6 Je Y, Giovannucci E. Coffee consumption and risk of endometrial cancer: findings from a large up-to-date meta-analysis. *Int J Cancer* 2012; **131:** 1700–10.
7 Bravi F, Tavani A, Bosetti C, Boffetta P, La Vecchia C. Coffee and the risk of hepatocellular carcinoma and chronic liver disease: a systematic review and meta-analysis of prospective studies. *Eur J Cancer Prev* (in press).
8 Jiang W, Wu Y, Jiang X. Coffee and caffeine intake and breast cancer risk: an updated dose-response meta-analysis of 37 published studies. *Gynecol Oncol* 2013; **129:** 620–29.
9 Corrêa TA, Monteiro MP, Mendes TM, et al. Medium light and medium roast paper-filtered coffee increased antioxidant capacity in healthy volunteers: results of a randomized trial. *Plant Foods Hum Nutr* 2012; **67:** 277–82.
10 Tai J, Cheung S, Chan E, Hasman D. Antiproliferation effect of commercially brewed coffees on human ovarian cancer cells in vitro. *Nutr Cancer* 2010; **62:** 1044–57.
11 Lubin JH, De Stefani E, Abnet CC, et al. Maté drinking and esophageal squamous cell carcinoma in South America: pooled results from two large multicenter case-control studies. *Cancer Epidemiol Biomarkers Prev* 2014; **23:** 107–16.
12 Castellsagué X, Muñoz N, De Stefani E, Victora CG, Castelletto R, Rolón PA. Influence of mate drinking, hot beverages and diet on esophageal cancer risk in South America. *Int J Cancer* 2000; **88:** 658–64.
13 Islami F, Pourshams A, Nasrollahzadeh D, et al. Tea drinking habits and oesophageal cancer in a high risk area in northern Iran: population based case-control study. *BMJ* 2009; **338:** b929.
14 Rapozo DC, Blanco TC, Reis BB, et al. Recurrent acute thermal lesion induces esophageal hyper proliferative premalignant lesions in mice esophagus. *Exp Mol Pathol* 2016; **1:** 1–10.
15 Li ZG, Shimada Y, Sato F, et al. Promotion effects of hot water on N-nitrosomethyl-benzylamine-induced esophageal tumorigenesis in F344 rats. *Oncol Rep* 2003; **10:** 421–26.

EXHIBIT “B”

International Agency for Research on Cancer

World Health Organization

Exhibit # 59726

Q&A on Monographs Volume 116: Coffee, maté, and very hot beverages

Questions about the Monographs

1. What does the IARC Monographs Programme do?

The Monographs Programme identifies and evaluates causes of cancer in humans based on the publically available scientific evidence. To date, more than 950 agents have been reviewed and classified.

2. What does the classification mean in terms of risk?

The IARC Monographs Programme seeks to classify cancer hazards, meaning the potential of any substance to cause cancer based on current knowledge. The classification includes evidence from epidemiological studies of real-world exposures to carcinogens in human populations. The classification does not indicate what level of risk exists to people's health associated with exposure to a classified hazard. For example, IARC has classified tobacco smoking as *carcinogenic to humans* (Group 1), but that classification does not indicate the increase in risk for each cigarette smoked.

For more information on the IARC classification, read the IARC Monographs Q&A.

Questions about coffee

3. What was the evaluation of coffee drinking?

Coffee drinking is *not classifiable as to its carcinogenicity to humans* (Group 3).

Many epidemiological studies showed that coffee drinking had no carcinogenic effects for cancers of the pancreas, female breast, and prostate, and reduced risks were seen for cancers of the liver and uterine endometrium.

For more than 20 other cancers, the evidence was inadequate to enable a conclusion to be made.

4. What are the main studies that were evaluated?

The most important studies evaluated were epidemiological cohort studies of people who reported their coffee drinking habits and were followed up for many years to see how many of them developed cancer and how that was related to their coffee consumption. There was also important evidence from epidemiological case–control studies and experimental studies in animals and cells in culture.

5. What is new since the previous evaluation?

Coffee drinking was evaluated by IARC in 1991 (Monographs Volume 51). At the time it was classified as *possibly carcinogenic to humans* (Group 2B), based on *limited evidence* from epidemiological studies that coffee causes bladder cancer. *Limited evidence* means that a positive association has been observed between exposure to the agent and cancer but that chance, bias, or confounding could not be ruled out. In the 1991 evaluation, there was also *evidence suggesting lack of carcinogenicity* for the breast and large intestine and *inadequate evidence* for other cancers. The evidence in experimental animals was *inadequate*.

Ex. 9

The current evaluation is based on a much larger and stronger body of evidence. Nearly 500 relevant epidemiological studies on more than 20 different types of cancer were identified.

Many epidemiological studies now available showed that coffee drinking had no carcinogenic effects for cancers of the pancreas, female breast, and prostate, and reduced risks were seen for cancers of the liver and uterine endometrium.

For more than 20 other cancers, the evidence was inadequate to enable a conclusion to be made.

The evidence that drinking coffee might cause bladder cancer, which was *limited* in the previous evaluation, has become weaker, and it is no longer possible to determine whether drinking coffee causes bladder cancer.

6. Why did IARC choose to re-evaluate coffee? Why was coffee seen as a high priority?

Coffee drinking was recommended as a high priority for re-evaluation by an international advisory group (IARC Advisory Group), for two main reasons. First, many new studies have been done in the past 25 years. Second, it was thought that the new studies might clarify the previous evaluation, which had indicated that coffee was *possibly carcinogenic to humans* (Group 2B), based on *limited evidence* for bladder cancer, but found *evidence suggesting lack of effect* for two other types of cancer.

7. How should governments or health agencies use these results?

Identification of a cancer hazard in the IARC Monographs is an important alert that exposure can cause cancer in exposed people. Therefore, the IARC Monographs provide scientific evidence for the World Health Organization, governments, and health agencies to consider in developing health guidelines and policies. However, the Monographs do not recommend what actions should be taken, as those remain the responsibility of the authorities concerned.

8. What types of coffee were evaluated?

Although many different kinds of coffee are available and coffee can be prepared in many different ways, most studies did not look at different kinds of coffee or different ways of preparing it. As a result, there is not enough information to enable conclusions to be made about any particular kind of coffee.

9. What about instant coffee, filter coffee, organic coffee, etc.? Does the way coffee is prepared change anything about the risk of consumption?

The chemical properties of coffee can differ depending on the kind of coffee tree it comes from, how it is processed and roasted, and how it is prepared for drinking. However, the studies that have been reported until now do not show consistent and robust differences in cancer risk for different kinds of coffee or different preparation methods.

10. Does the IARC classification mean that coffee is safe in terms of a potential link to cancer?

A Group 3 evaluation does not mean that a substance has been proven to be safe. It means that the existing scientific data do not enable a conclusion to be made about whether it causes cancer. While this was the case for coffee overall, it was possible to conclude that coffee is unlikely to cause certain cancers, including cancers of the breast, prostate, and pancreas. Reduced risks were seen for cancers of the liver and uterine endometrium.

For more than 20 other cancers, the evidence was inadequate to enable a conclusion to be made.

IARC, 150 Cours Albert Thomas, 69372 Lyon CEDEX 08, France - Tel: +33 (0)4 72 73 84 85 - Fax: +33 (0)4 72 73 85 75

11. How could there be a "downgrade" from the previous evaluation?

The human evidence that suggested a link between coffee drinking and bladder cancer in 1991 was classified as *limited* at that time. This meant that although a causal relationship was seen as credible, other explanations such as bias and confounding could not be excluded. Most importantly, many of the early positive studies did not adequately account for tobacco smoking, which is a major risk factor for bladder cancer and can be strongly correlated with coffee drinking. The majority of high-quality studies that have subsequently been published do not show consistent evidence that coffee consumption is associated with bladder cancer.

Question about tea

12. Has tea been evaluated?

Tea was not re-evaluated in this Monograph. IARC evaluated tea as *not classifiable as to its carcinogenicity to humans* (Group 3) in Monographs Volume 51, and this classification is still valid.

Questions about maté

13. What type of maté did IARC evaluate?

Maté is an infusion made from dried leaves of a South American shrub, *Ilex paraguariensis*. Maté is consumed mostly in South America. It is traditionally drunk very hot, using a metal straw. It may also be consumed warm or cold.

14. What is new since the previous evaluation?

When it was evaluated by IARC in 1991, hot maté drinking was classified as *probably carcinogenic to humans* (Group 2A), based on limited evidence from several epidemiological studies from South America that showed associations with cancer of the oesophagus. Maté, without further specification of temperature was evaluated as *not classifiable as to its carcinogenicity to humans* (Group 3). No cancer studies in animals were available at the time.

In the new evaluation, drinking maté that is not very hot was *not classifiable as to its carcinogenicity to humans* (Group 3). There is no specific evaluation for very hot maté, but it is now included in the evaluation of very hot beverages as *probably carcinogenic to humans* (Group 2A).

15. Why was maté a high priority?

Several epidemiological studies of maté drinking that have been conducted since the previous evaluation show the risk of oesophageal cancer increasing with the temperature of the drink. There are also several new experimental studies in animals.

With the availability of new data, the IARC Advisory Group recommended a re-evaluation focused on understanding whether the associations seen in earlier studies were due to maté itself or to the temperature of the drink.

IARC, 150 Cours Albert Thomas, 69372 Lyon CEDEX 08, France - Tel: +33 (0)4 72 73 84 85 - Fax: +33 (0)4 72 73 85 75

16. Why did IARC evaluate maté drinking in South America?

The first studies of maté drinking were conducted in an area of South America where the incidence of oesophageal cancer is higher than usual and maté drinking is common. Some studies suggested that maté drinking could be responsible for the increased risk of cancer in this area, but there could be other explanations, such as differences in diet and tobacco use and alcohol consumption.

17. How should governments or health agencies use these results?

The IARC Monographs provide scientific evidence for the World Health Organization, governments, and health agencies to consider in developing health guidelines and policies. However, the Monographs do not recommend what actions should be taken, as those remain the responsibility of the authorities concerned.

18. What are the main studies that IARC based the evaluation on?

The evaluation of maté is based mainly on nine epidemiological case–control studies in Argentina, Brazil, Paraguay, and Uruguay that investigated the association of maté drinking with cancer of the oesophagus. The participants in these studies were asked about their consumption of maté. In some studies they were also asked to describe the typical temperature at which they drank maté. A larger study that pooled data from five earlier ones included detailed statistical analyses of the amount and temperature of maté in relation to the risk of oesophageal cancer.

The carcinogenicity of maté has been studied in only one experiment with rats, where it was given as a drinking liquid.

19. Are these results linked to the temperature of the beverage or the maté itself?

Epidemiological studies found that cancer of the oesophagus is associated with drinking maté at "very hot" temperatures but not with drinking maté warm or cold. Experiments with rats and mice also found effects of very hot liquids but no carcinogenic effects of maté.

Questions about very hot beverages

20. Why did IARC evaluate very hot beverages?

Studies of other hot drinks, mainly tea, in several other countries, including China, the Islamic Republic of Iran, Japan, and Turkey, also found that the risk of oesophageal cancer may increase with the temperature of the drink.

Several experiments with rats and mice also found that very hot liquids can promote the development of tumours in experimental animals.

21. How hot is "very hot"?

Experimental studies with animals suggest that carcinogenic effects probably occur with drinking temperatures of 65 °C or above. In cancer epidemiological studies, people have been asked to describe the usual temperature of beverages they drink. In addition, surveys from regions with a high incidence of cancers of the oesophagus have found that the temperature of very hot drinks was more than 65 °C. Therefore, the definition of very hot beverages as temperatures of 65 °C or above comes from studies in animals and is also supported by real-world measurements of drinking temperatures of beverages. In contrast, the typical drinking temperature for tea and coffee in most parts of the world is below 65 °C.

IARC, 150 Cours Albert Thomas, 69372 Lyon CEDEX 08, France - Tel: +33 (0)4 72 73 84 85 - Fax: +33 (0)4 72 73 85 75

22. How can IARC be sure that it is the temperature, and not the beverage, that is a probable cause of oesophageal cancer?

A combined analysis of several epidemiological studies with 1400 cases of oesophageal cancer considered both the temperature and the amount of maté that people drank. The results showed that the risk of cancer increased with temperature, independent of the amount consumed. There were statistically significant increases in risk for drinking very hot maté, but not for drinking warm maté. One other epidemiological study investigated cold maté drinking and found no increased risk. Experiments with rats and mice also found that very hot water (at 65 °C) promoted the development of oesophageal tumours, whereas maté did not.

23. What kind of oesophageal cancer is related to drinking very hot beverages?

There are two types of cancers that arise in different parts of the oesophagus. Squamous cell cancer (from the upper part of the oesophagus) is the most common, accounting for 90% of cases globally, whereas adenocarcinoma (from the lower part of the oesophagus) accounts for 10%.

Smoking and alcohol drinking are risk factors for squamous cell cancer in many high-income countries. However, the majority of oesophageal squamous cell cancers occur in low- and middle-income countries. Most studies of very hot beverages evaluated by the Monographs were in low- and middle-income countries, but didn't specify the type of oesophageal cancer linked to drinking very hot beverages.

IARC, 150 Cours Albert Thomas, 69372 Lyon CEDEX 08, France - Tel: +33 (0)4 72 73 84 85 - Fax: +33 (0)4 72 73 85 75

EXHIBIT “C”

Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims - Final

This Document available in Hindi (**PDF (/downloads/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/UCM246969.pdf)**), Traditional Chinese (**PDF (/downloads/Food/GuidanceRegulation/UCM246965.pdf)**), Simplified Chinese (**PDF (/downloads/Food/GuidanceRegulation/UCM246966.pdf)**)

January 2009

Contains Nonbinding Recommendations

Additional copies are available from:
Office of Nutrition, Labeling and Dietary Supplements
Division of Nutrition Programs and Labeling HFS-830
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5001 Campus Drive
College Park, MD 20740
(Tel) 301-436-1450 (Updated phone: 240-402-1450)
http://www.cfsan.fda.gov/guidance.html

You may submit written or electronic comments regarding this guidance at any time. Submit written comments on the guidance to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to **http://www.regulations.gov (http://www.regulations.gov/)**. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Food Safety and Applied Nutrition
January 2009

Contains Nonbinding Recommendations

Table of Contents

Contains Nonbinding Recommendations

Guidance for Industry[1]
Evidence-Based Review System for the Scientific Evaluation of Health Claims

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate telephone number listed on the title page of this guidance.

I. Introduction

This guidance document is for industry. It represents the agency's current thinking on 1) the process for evaluating the scientific evidence for a health claim, 2) the meaning of the significant scientific agreement (SSA) standard in section 403(r)(3) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 343(r)(3)) and 21 CFR 101.14(c), and 3) credible scientific evidence to support a qualified health claim.

This guidance document describes the evidence-based review system that FDA intends to use to evaluate the publicly available scientific evidence for SSA health claims or qualified health claims on the relationship between a substance and a disease or health-related condition.[2] This guidance document explains the agency's current thinking on the scientific review approach FDA should use and is intended to provide guidance to health claim petitioners.[3]

The specific topics addressed in this guidance document are: (1) identifying studies that evaluate the substance/disease relationship, (2) identifying surrogate endpoints for disease risk, (3) evaluating the human studies to determine whether scientific conclusions can be drawn from them about the substance/disease relationship, (4) assessing the methodological quality of each human study from which scientific conclusions about the substance/disease relationship can be drawn, (5) evaluating the totality of scientific evidence, (6) assessing significant scientific agreement, (7) specificity of claim language for qualified health claims, and (8) reevaluation of existing SSA or qualified health claims.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency's guidances means that something is suggested or recommended, but not required.

back to top

II. Background

The Nutrition Labeling and Education Act of 1990 (NLEA) (Pub. L. 101-553) was designed to give consumers more scientifically valid information about foods they eat. Among other provisions, the NLEA directed FDA to issue regulations providing for the use of statements that describe the relationship between a substance and a disease ("health claims") in the labeling of foods, including dietary supplements, after such statements have been reviewed and authorized by FDA.[4] For these health claims, that is, statements about substance/disease relationships, FDA

has defined the term "substance" by regulation as a specific food or food component (21 CFR 101.14(a)(2)). An authorized health claim may be used on both conventional foods and dietary supplements, provided that the substance in the product and the product itself meet the appropriate standards in the authorizing regulation. Health claims are directed to the general population or designated subgroups (e.g., the elderly) and are intended to assist the consumer in maintaining healthful dietary practices.

In evaluating a petition for an authorized health claim, FDA considers whether the evidence supporting the relationship that is the subject of the claim meets the SSA standard. This standard derives from 21 U.S.C. 343 (r)(3)(B)(i), which provides that FDA shall authorize a health claim to be used on conventional foods if the agency "determines based on the totality of the publicly available evidence (including evidence from well-designed studies conducted in a manner which is consistent with generally recognized scientific procedures and principles), that there is significant scientific agreement among experts qualified by scientific training and experience to evaluate such claims, that the claim is supported by such evidence." This scientific standard was prescribed by statute for conventional food health claims; by regulation, FDA adopted the same standard for dietary supplement health claims. See 21 CFR 101.14(c).

The genesis of qualified health claims was the court of appeals decision in *Pearson v. Shalala* (*Pearson*). In that case, the plaintiffs challenged FDA's decision not to authorize health claims for four specific substance-disease relationships in the labeling of dietary supplements. Although the district court ruled for FDA (14 F. Supp. 2d 10 (D.D.C. 1998), the U.S. Court of Appeals for the D.C. Circuit reversed the lower court's decision (164 F.3d 650 (D.C. Cir.1999)). The appeals court held that the First Amendment does not permit FDA to reject health claims that the agency determines to be potentially misleading unless the agency also reasonably determines that a disclaimer would not eliminate the potential deception. The appeals court also held that the Administrative Procedure Act (APA) required FDA to clarify the "significant scientific agreement" (SSA) standard for authorizing health claims.

On December 22, 1999, FDA announced the issuance of its *Guidance for Industry: Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements* (64 Fed. Reg.17494). This guidance document was issued to clarify FDA's interpretation of the SSA standard in response to the court of appeals' second holding in *Pearson.*

On December 20, 2002, the agency announced its intention to extend its approach to implementing the *Pearson* decision to include health claims for conventional foods (67 Fed. Reg. 78002). Recognizing the need for a scientific framework for qualified health claims, the Task Force on "Consumer Health Information for Better Nutrition" was formed. The Task Force recognized that there could be significant public health benefits when consumers have access to, and use, more and better information in conventional food as well as dietary supplement labeling to aid them in their purchases, information that goes beyond just price, convenience, and taste, but extends to include science-based health factors. Armed with more scientifically based information about the likely health benefits of the foods and dietary supplements they purchase, consumers can make a tangible difference in their own long-term health by lowering their risk of numerous chronic diseases.

To maximize the public health benefit of FDA's claims review process, the Task Force's Final Report[(5)] provides a procedure to prioritize on a case-by-case basis all complete petitions according to several factors, including whether the food or dietary supplement that is the subject of the petition is likely to have a significant impact on a serious or life-threatening illness; the strength of the evidence; whether consumer research has been provided to show the claim is not misleading; whether the substance that is the subject of the claim has undergone an FDA safety review (i.e., is an authorized food additive, has been Generally Recognized as Safe (GRAS) affirmed, listed, or has received a letter of "no objection" to a GRAS notification); whether the substance that is the subject of the claim has been adequately characterized so that the relevance of available studies can be evaluated; whether the disease is defined and evaluated in accordance with generally accepted criteria established by a recognized body of qualified experts; and whether there has been prior review of the evidence or the claim by a recognized body of qualified experts.

As part of the Task Force's final report, FDA developed an interim evidence-based review system that the agency intended to use to evaluate the substance/disease relationships that are subjects of qualified health claims. In reviewing the December 22, 1999 SSA guidance document and the 2003 Task Force report, it became apparent to the agency that the components of the scientific review process for an SSA health claim and qualified health claim are very similar. Because of the similarity between the scientific reviews for SSA and qualified health claims, FDA intends to use the approach set out in this guidance for evaluating the scientific evidence in petitions that are submitted for an SSA health claim or qualified health claim. The evidence-based review system set out in this guidance will assist the agency in determining whether the scientific evidence meets the SSA standard or, if not, whether the evidence supports a qualified health claim. In addition to a science review, health claims undergo a regulatory review. Health claims that meet the SSA standard are authorized by publication of a final rule or an interim final rule in the Federal Register. For qualified health claims supported by credible evidence, FDA issues a letter regarding its intent to consider enforcement discretion.

Although this guidance replaces the *Guidance for Industry: Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements* (64 Fed. Reg. 17494), issued to clarify FDA's interpretation of the SSA standard in response to the court of appeals' second holding in *Pearson,* FDA believes this guidance continues to be consistent with the court's holding. The basic principles of SSA articulated in the 1999 guidance have not changed. A finding of SSA still requires the agency's best judgment as to whether qualified experts would likely agree that the scientific evidence supports the substance/disease relationship that is the subject of a proposed health claim. In fact, many of the explanations of SSA in this guidance are taken verbatim from the 1999 guidance. This guidance represents further scientific developments in the agency's approach to the review of scientific evidence rather than a change in its understanding of what constitutes SSA.

back to top

III. Evidence-Based Review System for the Scientific Evaluation of Health Claims

A. What is an Evidence-Based Review System?

An evidence-based review system is a systematic science-based evaluation of the strength of the evidence to support a statement. In the case of health claims, it evaluates the strength of the scientific evidence to support a proposed claim about a substance/disease relationship. The evaluation process involves a series of steps to assess scientific studies and other data, eliminate those from which no conclusions about the substance/disease relationship can be drawn, rate the remaining studies for methodological quality and evaluate the strength of the totality of scientific evidence by considering study types, methodological quality, quantity of evidence for and against the claim (taking into account the numbers of various types of studies and study sample sizes), relevance to the U.S. population or target subgroup, replication of study results supporting the proposed claim, and overall consistency of the evidence. After assessing the totality of the scientific evidence, FDA determines whether there is SSA to support an authorized health claim, or credible evidence to support a qualified health claim.

back to top

B. Identifying Studies That Evaluate the Substance/Disease Relationship

The agency considers the publicly available data and written information pertaining to the relationship between a substance and disease. FDA reviews studies that must be submitted in petitions seeking health claims (21 CFR 101.70). Through a literature search, the agency identifies additional studies that are relevant to the proposed health claim. Before the strength of the evidence for a substance/disease relationship can be assessed, FDA separates individual relevant articles on human studies from other types of data and information. FDA intends to focus its review

primarily on articles reporting human intervention and observational studies because only such studies can provide evidence from which scientific conclusions can be drawn about the substance/disease relationship in humans. Next, the agency considers a number of threshold questions in the review of the scientific evidence:

• *Have the studies specified and measured the substance that is the subject of the claim?* Studies should identify a substance that is measurable. A "substance" is defined as a specific food or component of food regardless of whether the food is in conventional food form or a dietary supplement. 21 CFR 101.14(a) (2). A food component can be, for example, a nutrient or dietary ingredient.[(6)] If the substance is to be consumed as a component of conventional food at decreased dietary levels, the substance must be a nutrient that is required to be included in the Nutrition Facts label (21 CFR 101.14(b)(2)). If the substance is to be consumed at other than decreased dietary levels, the substance must contribute taste, aroma, nutritive value,[(7)] or a technical effect listed in 21 CFR 170.3(o) to the food, and must be safe and lawful for use at the levels necessary to justify a claim (21 CFR 101.14(b)(3)).

• *Have the studies appropriately specified and measured the specific disease or health-related condition that is the subject of the claim?* "Disease or health-related condition" is defined as damage to an organ, part, structure, or system of the body such that it does not function properly (e.g., cardiovascular disease), or a state of health leading to such dysfunctioning (e.g., hypertension). 21 CFR 101.14(a) (5). Studies should identify a specific measurable disease or health-related condition by either measuring incidence, associated mortality, or validated surrogate endpoints that predict risk of a specific disease.

For example, cancer is a constellation of more than 100 different diseases, each characterized by the uncontrolled growth and spread of abnormal cells (American Cancer Society, 2004). Cancer is categorized into different types of diseases based on the organ and tissue sites (National Cancer Institute). Cancers at different organ sites have different risk factors, treatment modalities, and mortality risk (American Cancer Society, 2004). Both genetic and environmental (including diet) risk factors may affect the risk of different types of cancers. Risk factors may include a family history of a specific type of cancer, cigarette smoking, alcohol consumption, overweight and obesity, exposure to ultraviolet or ionizing radiation, exposure to cancer-causing chemicals, and dietary factors. The etiology, risk factors, diagnosis, and treatment for each type of cancer are unique (Hord et al., 2007; Milner et al., 2006). Since each form of cancer is a unique disease based on organ site, risk factors, treatment options, and mortality risk, FDA's current approach is to evaluate each form of cancer individually in a health claim or qualified health claim petition to determine whether the scientific evidence supports the potential substance-disease relationship for that type of cancer, which would constitute a disease under 21 CFR 101.14(a)(5). The agency has used this approach in several letters of enforcement discretion including **green tea and cancer dated June 30, 2005 (/Food/IngredientsPackagingLabeling/LabelingNutrition/ucm072774.htm)** (http://www.cfsan.fda.gov/~dms/qhc-gtea.html)*, **tomatoes/lycopene and various cancers dated November 8, 2005 (/Food/IngredientsPackagingLabeling/LabelingNutrition/ucm072760.htm)** (http://www.cfsan.fda.gov/~dms/qhclyco.html)*, **calcium and various cancers dated October 12, 2005 (/Food/IngredientsPackagingLabeling/LabelingNutrition/ucm072771.htm)** (http://www.cfsan.fda.gov/~dms/qhcca2.htm)* as well as the Federal Register notice entitled "Health Claims and Qualified Health Claims; Dietary Lipids and Cancer, Soy Protein and Coronary Heart Disease, Antioxidant Vitamins and Certain Cancers, and Selenium and Certain Cancers; Reevaluation" (72 Fed. Reg. 72738, December 21, 2007)

After considering these threshold issues, FDA categorizes the studies by type.

Intervention Studies

In an intervention study, subjects are provided the substance (food or food component) of interest (intervention group), typically either in the form of a conventional food or dietary supplement. The quality and quantity of the substance should be controlled for. In randomized controlled trials, subjects are assigned to an intervention group by chance. Individual subjects may not be similar to each other, but the intervention and control groups should be similar after randomization. Randomized controlled trials offer the best assessment of a causal relationship between a

substance and a disease because they control for known confounders of results (i.e., other factors that could affect risk of disease). Through random assignment of subjects to the intervention and control groups, these studies avoid selection bias -- that is, the possibility that those subjects most likely to have a favorable outcome, independent of an intervention, are preferentially selected to receive the intervention. Potential bias is also reduced by "blinding" the study so that the subjects do not know whether they are receiving the intervention, or "double blinding," in which neither the subjects nor the researcher who assesses the outcome knows who is in the intervention group and who is in the control group. By controlling the test environment, including the amount and composition of substance consumed and all other dietary factors, these studies also can minimize the effects of variables or confounders on the results.[8] Therefore, randomized, controlled intervention studies provide the strongest evidence of whether or not there is a relationship between a substance and a disease (Greer et al., 2000).

Furthermore, such studies can provide convincing evidence of a cause and effect relationship between an intervention and an outcome (Kraemer et al., 2005 at 113). Randomization, however, may result in unequal distribution of the characteristics of the subjects between the control and treatment groups (e.g., baseline age or blood [serum or plasma] LDL cholesterol levels are significantly different). If the baseline values are significantly different, then it is difficult to determine if differences at the end of the study were due to the intervention or to differences at the beginning of the study. When the substance is provided as a supplement, a placebo should be provided to the control group. When the substance is a food, it may not be possible to provide a placebo and therefore subjects in such a study may not be blinded. Although the study may not be blinded in this case, a control group is still needed to draw conclusions from the study.

Randomized controlled trials typically have either a parallel or cross-over design. Parallel design studies involve two groups of subjects, the test group and the control group, which simultaneously receive the substance or serve as the control, respectively. Cross-over design involves all subjects crossing over from the intervention group to the control group, and vice versa, after a defined time period.

Although intervention studies are the most reliable category of studies for determining a cause-and effect relationship, generalizing from the studies conducted on selected populations to different populations may not be scientifically valid. For example, if the evidence consists of studies showing an association between intake of a substance and reduced risk of juvenile diabetes, then such studies should not be extrapolated to the risk of diabetes in adults.

Observational Studies

Observational studies measure associations between the substance and disease. Observational studies lack the controlled setting of intervention studies. Observational studies are most reflective of free-living[9] populationsand may be able to establish an association between the substance and the disease. In contrast to intervention studies, observational studies cannot determine whether an observed relationship represents a relationship in which the substance caused a reduction in disease risk or is a coincidence (Sempos et al., 1999). Because the subjects are not randomized based on various disease risk factors at the beginning of the study, known confounders of disease risk need to be collected and adjusted for to minimize bias. For example, information on each subject's risk factors, such as age, race, body weight and smoking, should be collected and used to adjust the data so that the substance/disease relationship is accurately measured. Risk factors that need to be adjusted for are determined for each disease being studied. For example, the risk of cardiovascular disease increases with age; therefore, an adjustment for age is needed in order to eliminate potential confounding.

In determining whether the substance that is the subject of the claim has been measured appropriately, it is important to critically evaluate the method of assessment of dietary intake. Many observational studies rely on self-reports of diet (e.g., diet records, 24-hour recalls, diet histories, and food frequency questionnaires), which are estimates of food intake (National Research Council, 1989). Diet records are based on the premise that food weights provide an accurate estimation of food intake. Subjects weigh the foods they consume and record those values. The 24-hour recall method requires that subjects describe which foods and how much of each food they consumed during the prior

24-hour period. Diet histories use questionnaires or interviewers to estimate the typical diet of subjects over a certain period of time. A food frequency questionnaire is the most common dietary assessment tool used in large observational studies of diet and health. Validated food frequency questionnaires are more reliable in estimating "usual" intake of foods than diet records or 24-hour recall methods (Subar et al., 2001). The questionnaire asks participants to report the frequency of consumption and portion size from a list of foods over a defined period of time. One problem with the dietary intake assessment methods described above is that there may be bias in the self-reporting of certain foods. For example, individuals who are overweight tend to under-report their portion sizes (Flegal et al., 1999) and therefore the actual amount of substances consumed is often underestimated. If there are reliable biomarkers of intake[(10)] of a substance, these biomarkers are often measured rather than using self-reported intakes.

Observational studies may be prospective or retrospective. These types of studies are subject to different forms of bias (information and selection).[(11)] In prospective studies, investigators recruit subjects and observe them prior to the occurrence of the disease outcome. Prospective observational studies compare the incidence of a disease with exposure to the substance. In retrospective studies, investigators review the medical records of subjects and/or interview subjects after the disease has occurred. Retrospective studies are particularly vulnerable to measurement error and recall bias because they rely on subjects' recollections of what they consumed in the past. Because of the limited ability of observational studies to control for variables, they are often susceptible to confounders, such as complex substance/disease interactions.

Well-designed observational studies can provide useful information for identifying possible associations to be tested by intervention studies (Kraemer et al., 2005 at 107). In contrast to intervention studies, even the best-designed observational studies cannot establish cause and effect between an intervention and an outcome (Kraemer et al., 2005 at 114). However, as discussed above, intervention studies can test whether there is evidence to show a cause and effect between a substance and a reduced risk of a disease. Observational studies from which scientific conclusions can be drawn, in some situations, can be support for a substance/disease relationship for an SSA or qualified health claim. Each observational study design has its strength and weaknesses as discussed below (Sempos et al., 1999).

Cohort studies are prospective studies that compare the incidence of a disease in subjects who receive a specific exposure of the substance that is the subject of the claim with the incidence of the disease in subjects who do not receive that exposure. Because the intake of the substance precedes disease development, this study design ensures that the subjects are not consuming the substance in response to having the disease. Cohort studies can yield relative estimates of risk (Szklo and Nieto, 2000).[(12)] Cohort studies are considered to be the most reliable observational study design (Greer et al., 2000).

In*case-control studies*, subjects with a disease (cases) are compared to subjects who do not have the disease (controls).[(13)] Prior intake of the substance is estimated from dietary assessment methods for both cases and control. These retrospective studies often ask about food consumption at least 1 year prior to diagnosis of the disease, making it difficult to obtain an accurate estimate of intake. Furthermore, a key assumption is that food consumption has not been altered by the disease process or by knowledge of having the disease. Thus, the case-control study design does not control for changes in intake caused by or in response to the disease. Case-control studies can yield an odds ratio, which is an estimate of the relative risk of getting the disease (Szklo and Nieto, 2000).[(14)] Case-control studies are considered to be less reliable than cohort studies (Greer et al., 2000).

A *nested-case control or case-cohort* study uses subjects from a pre-defined cohort, such as the population of an ongoing cohort study. Cases are subjects diagnosed with the disease (e.g., lung cancer) in the cohort. In a nested-case control study, controls are subjects selected from individuals at risk each time a case (e.g., lung cancer) is diagnosed. In a case-cohort study, controls are selected randomly from the baseline cohort (Szklo and Nieto, 2000). Either a relative risk or odds ratio may be calculated in these types of studies. Nested-case control or case-cohort studies are considered less reliable than cohort studies but more reliable than case-control studies.

Cross-sectional studies usually involve collecting information on food consumption at a single point in time in individuals with and without a specific disease.(15) These studies can be useful for identifying possible correlates (i.e., by determining the correlation coefficient (16) between dietary intake of a substance and prevalence of a disease) and for providing baseline information for subsequent prospective studies (Kraemer et al., 2005 at 99-100). However, because dietary intake and disease status are measured at the same time, it is not possible to determine whether dietary intake of the substance is a factor affecting the risk of the disease or a result of having the disease. Cross-sectional studies calculate the prevalence of a disease based on exposure and this may be a measure of survival of the disease rather than the risk of developing the disease (Szklo and Nieto, 2000). Further, cross-sectional studies are considered to be a "relatively weak method of studying diet-disease associations" because they can be subject to significant potential measurement error regarding dietary intake due to inaccuracy of survey methods used and limited ability to control for dietary intake variations (Sempos et al., 1999). For these reasons, cross-sectional study results "have the potential to mislead as errors of interpretation are very common" (Kraemer et al., 1005 at 103). Cross-sectional studies are considered to be less reliable than cohort and case-control studies (Greer et al., 2000).

Ecological studies compare disease incidence across different populations. *Case reports* describe observations of a single subject or a small number of subjects. Ecological studies and case reports are the least reliable types of observational studies.

Research Synthesis Studies

Reports that discuss a number of different studies, such as review articles,(17) do not provide sufficient information on the individual studies reviewed for FDA to determine critical elements such as the study population characteristics and the composition of the products used. Similarly, the lack of detailed information on studies summarized in review articles prevents FDA from determining whether the studies are flawed in critical elements such as design, conduct of studies, and data analysis. FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. Therefore, FDA intends to use review articles and similar publications(18) to identify reports of additional studies that may be useful to the health claim review and as background about the substance/disease relationship. If additional studies are identified, the agency intends to evaluate them individually. Most meta-analyses,(19) because they lack detailed information on the studies summarized, will only be used to identify reports of additional studies that may be useful to the health claim review and as background about the substance-disease relationship. FDA, however, intends to consider as part of its health claim review process a meta-analysis that reviews all the publicly available studies on the substance/disease relationship. The reviewed studies should be consistent with the critical elements, quality and other factors set out in this guidance and the statistical analyses adequately conducted.

Animal and *in vitro* Studies

FDA intends to use animal and *in vitro* studies as background information regarding mechanisms that might be involved in any relationship between the substance and disease. The physiology of animals is different than that of humans. *In vitro* studies are conducted in an artificial environment and cannot account for a multitude of normal physiological processes such as digestion, absorption, distribution, and metabolism that affect how humans respond to the consumption of foods and dietary substances (IOM, 2005). Animal and *in vitro* studies can be used to generate hypotheses, investigate biological plausibility of hypotheses, or to explore a mechanism of action of a specific food component through controlled animal diets; however, these studies do not provide information from which scientific conclusions can be drawn regarding a relationship between the substance and disease in humans.

back to top

C. Identifying Surrogate Endpoints of Disease Risk

Surrogate endpoints are risk biomarkers[(20)] that have been shown to be valid predictors of disease risk and therefore may be used in place of clinical measurements of the onset of the disease in a clinical trial (Spilker, 1991). Because a number of diseases develop over a long period of time, it may not be possible to carry out the study for a long enough period to see a statistically meaningful difference in the incidence of disease among study subjects in the treatment and control groups.

These are examples of surrogate endpoints of disease risk accepted by the National Institutes of Health and/or FDA's Center for Drug Evaluation and Research: (1) serum low-density lipoprotein (LDL) cholesterol concentration, total serum cholesterol concentration, and blood pressure for cardiovascular disease; (2) bone mineral density for osteoporosis; (3) adenomatous colon polyps for colon cancer; and (4) elevated blood sugar concentrations and insulin resistance for type 2 diabetes.

There can be multiple pathways to a specific disease, such as cardiovascular disease. Therefore, the accepted surrogate endpoints that are involved in a single pathway may not be applicable to certain substances that are involved in a different pathway. For example, the long chain omega-3 fatty acids generally have no effect on serum LDL cholesterol levels, and studies suggest that these fatty acids alter cardiovascular risk through a different pathway. Therefore, LDL cholesterol levels cannot be used in evaluating the relationship between the long chain omega-3 fatty acids and risk of cardiovascular disease.

back to top

D. Evaluating Human Studies

Under the evidence-based review approach set out in this guidance, FDA intends to evaluate each individual human study to determine whether any scientific conclusions about the substance/disease relationship can be drawn from the study. Certain critical elements of a study, such as design, data collection, and data analysis, may be so seriously flawed that they make it impossible to draw scientific conclusions from the study. FDA does not intend to use studies from which it cannot draw any scientific conclusions about the substance/disease relationship, and plans to eliminate such studies from further review. Below are examples of questions that the agency intends to consider whether scientific conclusions can be drawn from an intervention or observational study about the substance/disease relationship.

Intervention Studies

• *Were the study subjects healthy or did they have the disease that is the subject of the health claim?* Health claims involve reducing the risk of a disease in people who do not have the disease that is the subject of the claim. FDA considers evidence from studies with subjects who have the disease that is the subject of the claim only if it is scientifically appropriate to extrapolate to individuals who do not have the disease. That is, the available scientific evidence demonstrates that (1) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations and (2) the substance affects these mechanisms in the same way in both diseased and healthy people. If such evidence is not available, the agency cannot draw any scientific conclusions from studies that used subjects that have the disease that is the subject of the health claim to evaluate the substance/disease relationship and, therefore, the agency does not intend to use these studies to evaluate the substance/disease relationship. On the other hand, if, for example, FDA was reviewing a health claim on reduction of risk of coronary heart disease, it would consider studies that include individuals who have an unrelated disease (e.g., osteoporosis) or are at risk (e.g., elevated LDL cholesterol levels) of getting the disease that is the subject of the claim.

• *Was the disease that is subject of the claim measured as a "primary" endpoint?* Intervention studies screen for prevalent cases of the disease at the beginning of the study to minimize bias. For example, intervention studies evaluating the recurrence of colorectal polyps prescreen the subjects to ensure there are no existing colorectal polyps

at the onset of the intervention study. Intervention studies may evaluate the outcomes of other diseases as secondary endpoints, but do not screen for these diseases at the onset of the study. For example, a study evaluating the recurrence of colorectal polyps may also evaluate the incidence of prostate cancer; however, because the prostate cancer endpoint is not the primary endpoint, the study would not screen the subjects to ensure that they are free of prostate cancer before enrolling them. Consequently, the results with respect to prostate cancer may be biased due to an uneven distribution of cases of prostate cancer between the treatment and placebo groups at the beginning of the study. Uneven distribution of important patient or disease characteristics between groups may lead to mistaken interpretation (Spilker, 1991); therefore, scientific conclusions about a disease endpoint cannot be drawn from a study unless the study evaluates that outcome as a primary endpoint.

• *Did the study include an appropriate control group?* An appropriate control group represents study subjects who did not receive the substance. If an appropriate control group is not included, then it is not possible to ascertain whether changes in the endpoint of interest were due to the substance or due to unrelated and uncontrolled extraneous factors (Spilker, 1991; Federal Judicial Center, 2000). Without an appropriate control group, scientific conclusions cannot be drawn about a substance/disease relationship and, therefore, the agency does not intend to use these studies to evaluate the substance/disease relationship.

When the intervention study involves providing a whole food rather than a food component, the experimental and control diets should be similar enough that the relationship between the substance and disease can be evaluated. For example, if the substance is a specific type of fatty acid, then the composition of the experimental and control diets should be similar for all food components, except that particular fatty acid. Scientific conclusions cannot be drawn about the relationship between a substance and a disease when the amounts of other substances that are known to affect the risk of the disease that is subject of the claim are different between the control and experimental diets.

• *Was the study designed to measure the independent role of the substance in reducing the risk of a disease?* When the substance is a food component, it may not be possible to accurately determine its independent effects when whole foods or multi-nutrient supplements are provided to the intervention group. For example, if the claim is about a relationship between lutein and age-related macular degeneration (AMD), then scientific conclusions cannot be drawn from a study in which the intervention group received spinach or multi-nutrient supplements that contain other substances (e.g., vitamin C, vitamin E, and zinc) that have been suggested to have a role in protecting against AMD. As another example, if the substance is a fatty acid that has been shown to alter blood cholesterol levels, but the levels of other food components (e.g., cholesterol) known to affect cholesterol levels markedly vary between the intervention and control diets, then it is not possible to determine the independent effect of the fatty acid.

• *Were the relevant baseline data (e.g., on the surrogate endpoint) significantly different between the control and intervention group?* If the baseline values for the endpoint being measured are significantly different, then it is difficult to interpret the findings of the intervention. For example, in a study of the effects of a low-sodium diet on the risk of cardiovascular disease, having baseline blood pressure levels higher in the intervention group than in the control group would lead to uncertainty as to whether any observed effect resulted from the difference in the sodium intake between the two groups. Providing a "lead-in"[(21)] diet or a "wash-out" period[(22)] for studies with a cross-over design for an adequate duration prior to randomization can help reduce the likelihood of different baseline values.

• *How were the results from the intervention and control groups statistically analyzed?* Statistical analysis of the study data is a critical factor because it provides the comparison between subjects consuming the substance and those not consuming the substance, to determine whether there is a reduction in risk of the disease. Furthermore, when conducting statistical analyses among more than two groups, the data should be analyzed by a test designed for multiple comparisons (e.g., Bonferroni, Duncan). Thus when statistical analyses are not performed between the control and intervention group or are conducted inappropriately, scientific conclusions cannot be drawn about the role of the substance in reducing the risk of the disease and, therefore, the agency does not intend to use such studies to evaluate the substance/disease relationship.

• *What type of biomarker of disease risk was measured?* As discussed above, when the study does not measure disease incidence or associated mortality, then surrogate endpoints are essential for measuring risk. Scientific conclusions cannot be drawn about the relationship between the substance and risk of the disease if the risk biomarker is not a surrogate endpoint (see discussion above in Section III.C). The agency does not intend to use such studies from which scientific conclusions cannot be drawn in its evaluation of the substance/disease relationship.

• *How long was the study conducted?* Studies that use a surrogate endpoint should be conducted long enough to ensure that any change in the endpoint is in response to the dietary intervention. If the study is run for a short time period such that the effects of the substance cannot be evaluated, then scientific conclusions cannot be drawn about the relationship between the substance and the disease and, therefore, the agency does not intend to use such a study to evaluate the substance/disease relationship. For example, FDA has considered 3 weeks to be the minimum duration for evaluating the effect of an intervention with various saturated fats on serum LDL cholesterol concentration (Kris-Etherton and Dietschy, 1997)

• *If the intervention involved dietary advice, was there proper follow-up to ascertain whether the advice resulted in altered intake of the substance?* When the dietary intervention involves dietary advice rather than a prescribed diet administered under a controlled condition, there should be some type of assessment of the changes in intake of the substance (e.g., dietary assessment or measurement of a biomarker of intake in response to dietary advice). Without some type of assessment of whether the dietary advice resulted in a change in intake of the substance, scientific conclusions cannot be drawn about the substance/disease relationship and, therefore, the agency does not intend to use studies that lack such an assessment to evaluate the substance/disease relationship.

• *Where were the studies conducted?* It is important that the study population is relevant to the general U.S. population or the population subgroup identified in the proposed claim. Thus, FDA evaluates each study to determine if the study population lives in an area where malnutrition or inadequate intakes of the specific substance is common, and/or where the prevalence or etiology of the disease that is the subject of the claim is not similar to that in the United States. For certain countries, there may be risk factors of a specific disease that are not relevant to disease risk in the United States (e.g., risk factors for gastric cancer in certain Asian countries). Differences in nutrition, diet, and disease risk factors between the United States and the country where a study was done may mean that the study results cannot be extrapolated to the U.S population or population subgroup. For example, scientific conclusions about the comparatively well-nourished U.S. population cannot be drawn from studies in subjects that are malnourished. Nutrient status and metabolism can be severely altered when an individual is malnourished, and therefore the effect of the substance on a particular surrogate endpoint may be very different between a malnourished and well-nourished individual (Shils et al., 2006). Scientific conclusions cannot be drawn from studies conducted in countries or regions where inadequate intake of the substance is common since a response to the intake of the substance may be due to the correction of a nutrient deficiency for which health claims are not intended.

Furthermore, conclusions cannot be drawn from studies conducted in countries or regions where the etiology of the disease is very different than in the United States. For example, major risk factors for gastric cancer in Japan (high salt intake and Helicobacter pylori (H. pylori) infection) are significantly more prevalent than in the United States. Therefore, it is not appropriate to extrapolate from data on a Japanese population concerning the relationship between a substance and gastric cancer to reach conclusions about potential effects on the U.S. population.

Observational Studies

• *What type of information was collected?* Biological samples (e.g., blood, urine, tissue, or hair) should be used to establish intake of a substance only if a dose-response relationship has been demonstrated between intake of the substance and the level of the substance (or a metabolite of the substance) in the biological sample. There should be evidence to demonstrate a strong correlation[(23)] between the intake level of the substance and the level of the substance or a metabolite in the biological sample (e.g., selenium intake and serum selenium concentration). If the correlation is weak for a specific biological sample, then scientific conclusions cannot be drawn from studies that used

that biological sample as a biomarker of intake. Biological samples in case-control studies should not be used to establish intake of the substance since the metabolism or concentration of the substance may be altered in subjects as a result of the disease.

• *Were scientifically acceptable and validated dietary assessment methods used to estimate intake of the substance?* A single 24-hour diet recall or diet record is generally regarded as an inadequate method for assessing an individual's usual intake of a substance, although it may be useful for assessing mean intake of a group. A diet history involves extensive interviews with the study subjects. However, diet histories are also usually inadequate for assessing intake of a substance since respondents are asked to make judgments about intakes of usual foods and the amounts eaten. A food frequency questionnaire contains a limited number of food items and is inadequate for assessing intake of a substance if the major sources of the substance are not included in the questionnaire. Food frequency questionnaires also do not always account for different varieties of a particular food or different cooking methods. Because of these limitations, validation of the food frequency questionnaire method to assess food intake is essential in order to be able to draw conclusions from the scientific data, as the failure to validate may lead to false associations between dietary factors and diseases or disease-related markers.[(24)]

• *Did the observational study evaluate the relationship between a disease and a food or a food component?* Because observational studies estimate intake of a whole food based on recorded dietary intake methods such as food frequency questionnaires, diet recalls, or diet records, a common weakness of observational studies is the limited ability to ascertain the actual intake of the substance for the population studied. Furthermore, if the substance is a food component rather than a whole food, there is an additional estimation of the amount of the food component that is present in the individual foods. The content of foods' components can vary based on factors such as soil composition, food processing/cooking procedures, or storage (duration, temperature). Thus, it is difficult to ascertain an accurate amount of the food component consumed based on reports of dietary intake of whole foods.

In addition, the whole food and products that include several food components, e.g., multi-nutrient dietary supplements, contain not only the food component that is the subject of the claim, but also other food components that may be associated with the metabolism of the food component of interest or the pathogenesis of the disease or health-related condition. Because whole foods and products such as multi-nutrient dietary supplements consist of many food components, it is difficult to study the food components in isolation (Sempos et al., 1999). For studies based on recorded dietary intake of whole foods or multiple food components, it is not possible to accurately determine whether any observed effects of the food component that is the subject of the claim on disease risk were due to: (1) that food component alone; (2) interactions with other food components; (3) other food components acting alone or together; or (4) decreased consumption of other substances contained in foods displaced from the diet by the increased intake of foods rich in the food component of interest (See Sempos et al. (1999), Willett (1990) and Willett (1998) regarding the complexity of identifying the relationship between a specific food component within a food and a disease).

In fact, evidence demonstrates that in a number of instances, observational studies based on the recorded dietary intake of conventional foods may indicate a benefit for a particular nutrient with respect to a disease, but it is subsequently demonstrated in an intervention study that the nutrient-containing dietary supplement does not confer a benefit or actually *increases* risk of the disease (Lichtenstein and Russell, 2005). For example, previous observational studies reported an association between fruits and vegetables high in beta-carotene and a reduced risk of lung cancer (Peto et al., 1981). However, subsequent intervention studies, the Alpha-Tocopherol and Beta Carotene Prevention Study (ATBC) and the Carotene and Retinol Efficiency Trial (CARET), demonstrated that beta-carotene supplements increase the risk of lung cancer in smokers and asbestos-exposed workers, respectively (The Alpha-Tocopherol and Beta Carotene Cancer Prevention Study Group, 1994; Omenn et al., 1996). These studies illustrate that the effect of a nutrient provided as a dietary supplement exhibits different health effects compared to when it is consumed among many other food components. Furthermore, these studies demonstrate the potential public health risk of relying on results from epidemiological studies, in which the effect of a nutrient is based on recorded dietary intake of conventional foods as the sole source for concluding that a relationship exists between a specific nutrient and disease

risk; the effect could actually be harmful. For the above reasons, scientific conclusions from observational studies cannot be drawn about a relationship between a food component and a disease. Observational studies, however, can be used to measure associations between a whole food and a disease.(25)

back to top

E. Assessing the Methodological Quality of Studies

For the studies that are not eliminated during the earlier evaluation, FDA intends to independently rate each such study for methodological quality. Studies can receive a high, moderate, or low quality rating. FDA intends to base this quality rating on several factors related to study design, data collection, the quality of the statistical analysis, the type of outcome measured, and study population characteristics other than relevance to the U.S. population (e.g., selection bias and the provision of important subject information [e.g., age, smokers]). If the scientific study adequately addressed all or most of the above factors, FDA plans to give it a high methodological quality rating. FDA plans to give moderate or low quality ratings based on the extent of the deficiencies or uncertainties in the quality factors. Studies that are so deficient in quality that they receive a low quality rating are studies from which scientific conclusions cannot be drawn about the substance/disease relationship and are eliminated from further review.

Examples of factors FDA intends to consider in assessing the methodological quality of individual studies remaining at this point in the scientific evaluation approach set out in this guidance include the following:

Intervention Studies

• *Were the studies randomized and blinded and was a placebo provided?* Appropriate randomization eliminates intrinsic and/or extrinsic factors, other than the substance, that could have an influence on the outcome of the study. Blinding is especially important when the endpoint can be influenced by a subject's awareness that he or she is receiving something that may be beneficial. Blinding would be critical when the outcome measure is cognitive performance, mental status (e.g. memory, depression), or behavior. Including a placebo in a supplementation trial prevents the subject from knowing whether he or she is receiving the substance or not.

• *Were inclusion/exclusion criteria and key information on the characteristics of the study population provided?* For instance, were healthy or high-risk subjects allowed to take medications that can affect the disease that is subject of the claim during the study? If so, was the proportion of subjects taking medications similar between the control and intervention groups?

• *Was subject attrition (subjects leaving the study before the study is completed) assessed, explained in the article reporting the study, and reasonable?* If there were a marked number of drop-outs, then it would be important to know why subjects dropped out and how the drop-outs affected the number and composition of the intervention and placebo group.

• *How was compliance with the study protocol verified?* Intervention studies should include a mechanism for verifying that the subjects followed the study protocol. For example, a supplementation trial should have a mechanism for determining how frequently the subjects took their supplements. It would be important to know 1) if the subjects took all of the supplements provided by the study or only a portion and 2) what proportion of the subjects for each group took less than the directed amount.

• *Was statistical analysis conducted on baseline data for the all subjects initially enrolled in the study or only those who completed the study?* If there were a marked number of drop-outs which, in turn, affected the composition of the intervention groups differently from the placebo groups, then it would be important to determine if statistical analysis on baseline data was conducted for all subjects initially enrolled in the study or only for those who completed the study.

• *Did the study measure disease incidence or a surrogate endpoint of disease risk?* While surrogate endpoints of disease risk have been validated, they are not as accurate as measuring the actual onset of a disease. This quality issue would also apply to observational studies.

• *How was the onset of a disease determined*? When disease incidence is the endpoint being measured, it is important that the disease that is subject of the claim is confirmed either through medical records and/or pathology reports. Relying on less specific records, such as death certificates, is not sufficient. This quality issue would also apply to observational studies.

Observational Studies

• *Was there an adequate adjustment for confounders of disease risk?* Several aspects of a substance/disease relationship may give rise to confounders. Therefore, it is important to adjust for confounders of the disease of interest so that observed effects on risk of disease that may be due to confounders are not incorrectly attributed to the substance of interest. For example, there can be multiple non-dietary risk factors for a disease (e.g., smoking, body mass index, and age for hypertension). Therefore, when evaluating the relationship between sodium and blood pressure, an adjustment of the risk analysis should be made based on age, smoking, body mass index and age.

• *What type of dietary assessment method was used to estimate dietary intake?*Validated food frequency questionnaires are more reliable in estimating "usual" intake of foods compared to diet records or 24-hour recall methods. See Section III.B.

back to top

F. Evaluating the Totality of Scientific Evidence

Under the approach set out in this guidance, at this point, FDA intends to evaluate the results of the studies from which scientific conclusions can be drawn and rate the strength of the total body of publicly available evidence. The agency plans to conduct this evaluation by considering the study type (e.g., intervention, prospective cohort, case-control, cross-sectional), methodological quality rating previously assigned, number of the various types of studies and sample sizes, relevance of the body of scientific evidence to the U.S. population or target subgroup, whether study results supporting the proposed claim have been replicated[(26)], and the overall consistency[(27)],[(28)] of the total body of evidence. Based on the totality of the scientific evidence, FDA determines whether such evidence meets the SSA standard or whether such evidence is credible to support a qualified health claim for the substance/disease relationship.

Within each study type, the studies are reviewed for:

- *Number* of studies and number of subjects per group
- *Methodological quality* (high, moderate, or low).
- *Outcome* (beneficial effect, no effect, adverse effect) of the studies within each study type. For the outcome of an intervention study to demonstrate an effect, the intervention group should be statistically significantly different from the control group ($P < 0.05$). For observational studies, confidence intervals (CI) for risk are significant when the value is less than or greater than "1". Many studies analyze for the statistical significance of the linear relationship (P for trend) between the substance and the disease. While this trend may be significant ($P<0.05$), the difference in risk between subjects at the various levels of intake (e.g., tertiles, quartiles or quintiles of intake)[(29)] may not be significant. In that case, the studies show no effect. Evaluation of the size of the effect (e.g., percent reduction in LDL cholesterol) may be useful for comparing effects within a study (e.g., relative effect of two forms of the substance or the relative effect of frequency of consumption).

- In general, the greater the *consistency* among the studies in showing a beneficial relationship, the greater the level of confidence that a substance/disease relationship exists. Conflicting results do not disprove an association (because the elements of the study design may account for the lack of an effect in negative studies) but tend to weaken confidence in the strength of the association. The greater the magnitude of the beneficial effect, the more likely the association may exist.
- *Relevance* to the general U.S. population. For example,

  To what extent did the studies that showed a benefit include populations that represent the general U.S. population or a population subgroup (e.g., elderly, women)?

  Did the studies only include subjects with unique lifestyles (e.g., smokers, vegetarians)?

  Do the studies suggest that the intake level of the substance that provides a benefit significantly exceeds usual intakes in the United States?

FDA evaluates whether the totality of the evidence supports a claim for the entire U.S. population or just a subgroup. If the evidence only supports a claim for a subgroup, that information would be set out in the claim. If the substance is one that must be used for risk reduction at much higher levels than the normal U.S. intake, that information would also be reflected in the claim.

In general, intervention studies provide the strongest evidence for the claimed effect, regardless of existing observational studies on the same relationship. Intervention studies are designed to avoid selection bias and avoid findings that are due to chance or other confounders of disease (Sempos et al., 1999). Although the evaluation of substance/disease relationships often involves both intervention and observational studies, observational studies generally cannot be used to rule out the findings from more reliable intervention studies (Sempos et al., 1999). One intervention study would not be sufficient to rule out consistent findings of observational studies. However, when several randomized, controlled intervention studies are consistent in showing or not showing a substance/disease relationship, they trump the findings of any number of observational studies (Barton, 2005). This is because intervention studies are designed and controlled to test whether there is evidence of a cause and effect relationship between the substance and the reduced risk of a disease, whereas observational studies are only able to identify possible associations. There are numerous examples -- such as vitamin E and CVD and beta-carotene and lung cancer -- where associations identified in observational studies have been publicized. However, when randomized, controlled intervention studies were later conducted to test these possible associations, the intervention studies found no evidence to support the relationships (Lichtenstein and Russell, 2005).

back to top

G. Assessing Significant Scientific Agreement

Significant scientific agreement refers to the extent of agreement among qualified experts in the field. On the continuum of scientific evidence that extends from very limited to inconclusive evidence, SSA lies closer to consensus. FDA's determination of SSA represents the agency's best judgment as to whether qualified experts would likely agree that the scientific evidence supports the substance/disease relationship that is the subject of a proposed health claim. The SSA standard is intended to be a strong standard that provides a high level of confidence in the validity of the substance/disease relationship. SSA means that the validity of the relationship is not likely to be reversed by new and evolving science, although the exact nature of the relationship may need to be refined. SSA does not require a consensus based on unanimous and incontrovertible scientific opinion. SSA occurs well after the stage of emerging science, where data and information permit an inference, but before the point of unanimous agreement within the relevant scientific community that the inference is valid.

For qualified experts to reach an informed opinion regarding the validity of a claim, the data and information that pertain to the claim must be available to the relevant scientific community. A finding of SSA then derives from the conclusion that there is a sufficient body of relevant, publicly available scientific evidence that shows consistency across different studies and among different researchers. The usual mechanism to show that the evidence is available to qualified experts is that the data and information are published in peer-reviewed scientific journals. The value of an expert's opinion will be limited if he or she did not have access to all the evidence.

In determining whether there is significant scientific agreement, FDA takes into account the viewpoints of qualified experts outside the agency, if evaluations by such experts have been conducted and are publicly available. For example, FDA intends to take into account:

- documentation of the opinion of an "expert panel" that is specifically convened for this purpose by a credible, independent body;
- the opinion or recommendation of a federal government scientific body such as the National Institutes of Health (NIH) or the Centers for Disease Control and Prevention (CDC); or the National Academy of Sciences (NAS);
- the opinion of an independent, expert body such as the Committee on Nutrition of the American Academy of Pediatrics (AAP), the American Heart Association (AHA), American Cancer Society (ACS), or task forces or other groups assembled by the National Institutes of Health (NIH);
- review publications that critically summarize data and information in the secondary scientific literature.

FDA accords the greatest weight to the conclusions of federal government scientific bodies, especially when the evidence for the validity of a substance/disease relationship has been judged by such a body to be sufficient to justify dietary recommendations to the public. When the validity of a substance/disease relationship is supported by the conclusions of federal government scientific bodies, FDA typically finds that significant scientific agreement exists. Conclusions of other expert bodies may also be relevant to support a determination of SSA. Although reviews by individual outside experts are considered in assessing SSA, evidence from such reviews alone would not necessarily support a conclusion that the standard has been met, especially if the conclusions of such reviews were not supported by available assessments of the same body of evidence from federal scientific bodies, expert panels, or independent expert bodies. Reviews by outside experts or expert panels are most useful when there is a reasonable basis to conclude that they represent the larger group of qualified experts in the field. Most importantly, the relevance of an outside expert review depends on whether the evidence examined applies to the claim in terms of considerations such as specification and measurement of the substance and the disease.

When conclusions from qualified experts are not available (for instance, if the data supporting a proposed health claim are relatively new and have not yet been reviewed by an independent expert panel or body), a compelling and relevant body of evidence may nonetheless cause the agency to conclude that significant scientific agreement exists. Because each situation may differ with the nature of the claimed substance/disease relationship, it is necessary to consider both the extent of agreement and the nature of the disagreement on a case-by-case basis. If scientific agreement were to be assessed under arbitrary quantitative or rigidly defined criteria, the resulting inflexibility could cause some valid claims to be disallowed where the disagreement, while present, is not persuasive.

Application of the significant scientific agreement standard is intended to be objective, in relying upon a body of sound and relevant scientific data; flexible, in recognizing the variability in the amount and type of data needed to support the validity of different substance/disease relationships; and responsive, in recognizing the need to re-evaluate data over time as research questions and experimental approaches are refined.

back to top

H. Specificity of the Claim Language for Qualified Health Claims

When the evidence for a substance-disease relationship is credible but does not meet the SSA standard, then the proposed claim for the relationship should include qualifying language that identifies limits to the level of scientific evidence to support the relationship.

The health claim language should reflect the level of scientific evidence with specificity and accuracy. However, gaps in the scientific evidence may sometimes limit the information that can be included in the claims. For example, when the scientific evidence is limited but credible, it may not be possible for the qualified health claim to identify an amount of the substance that is associated with a reduced risk of the disease.

Under FDA's health claim regulations, a health claim must specify the daily dietary intake of the substance necessary to achieve the claimed effect when there is no regulation defining what constitutes a "high" level of the substance in food (21 CFR 101.14(d)(2)(vii)). FDA has defined "high" in its nutrient content claim regulations as meaning that the food contains 20% or more of the Daily Value of the substance (21 CFR 101.54(b)). Therefore, when no Daily Value for the substance has been established, the agency cannot establish a definition for a "high" level of the substance. When the substance that is the subject of the claim has no Daily Value, FDA determines the daily dietary intake necessary to achieve the claimed effect whenever the available evidence is sufficient to make such a determination possible. See, e.g., 21 CFR 101.83(c)(2)(G) (health claim regulation for plant sterol/stanol esters and reduced risk of coronary heart disease). However, there are times when the credible evidence for the risk reduction effect is not specific enough for FDA to identify even a possible level of intake for the general U.S. population. See FDA's September 8, 2004, letter of enforcement discretion for qualified health claim about omega-3 fatty acids and reduced risk of coronary heart disease (Martek petition)

When there is credible evidence available to suggest a relationship between the substance and disease, it is important to determine whether the substance has an independent role in the relationship or whether its role is based on the inclusion or replacement (i.e., substitution) of other substances. An example of where the evaluation of the independent role of a substance can be challenging is when the substance is a conventional food or macronutrient (e.g., fat or carbohydrate). In studies evaluating the possible health effects of a conventional food or macronutrient, the inclusion of either in the diet usually requires the removal of other conventional foods or macronutrients (i.e., substitution to yield isocaloric diets). If it is determined that the substance does not play an independent role and/or requires the reduction or inclusion of another substance to show a beneficial effect, the claim language will reflect this finding.

back to top

I. Reevaluation of Existing SSA or Qualified Health Claims

FDA may reevaluate a health claim in response to a petitioner or on its own initiative, and when it does so it intends to use the scientific evaluation process described above. To maximize the public health benefit of its health claims review, FDA intends to evaluate new information that becomes available to determine whether it necessitates a change to an existing SSA or qualified health claim. For example, scientific evidence may become available that will (1) support the revision of claim language for an SSA or qualified health claim, (2) support change of an SSA claim to a QHC or support change of a QHC to an SSA claim, or (3) raise safety concerns about the substance that is the subject of a health claim or otherwise no longer support a health claim (SSA or QHC).

back to top

IV. References

- American Cancer Society, Cancer Facts and Figures, 2004.
- The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *New England Journal of Medicine* 1994;

330:1029-1035.

- Barton S. Which clinical studies provide the best evidence? The best RCT still trumps the best observational study. *British Medical Journal* 2000; 321:255-256.
- Cade J, Thompson R, Burley V, Warm D. Development, validation and utilization of food-frequency questionnaires – a review. *Public Health Nutrition* 2002; 5:567-587.
- Federal Judicial Center, Reference Manual on Scientific Evidence, Second Edition, 2000.
- Flegal KM. Evaluating epidemiological evidence of the effects of food and nutrient exposures. *American Journal of Clinical Nutrition* 1999; 69:1339S-1344S.
- Greer N, Mosser G, Logan G, Halaas GW. A practical approach to evidence grading. *Joint Commission Journal on Quality Improvements* 2000; 26:700-712.
- Hill AB. The environment and disease: association or causation? *Proceedings of the Royal Society of Medicine* 1965; 58:295-300
- Hord NG, Fenton JI. Context is everything: mining the normal and preneoplastic microenvironment for insights into the diet and cancer risk conundrum. *Molecular Nutrition and Food Research* 2007; 51:100-106.
- IOM, Institute of Medicine. Dietary Supplements: A Framework for Evaluating Safety. National Academies Press, Washington, DC. 2005.
- Kraemer HC, Lowe KK, Kupfer DJ. To Your Health: How to Understand What Research Tell Us About Risk. Oxford University Press, 2005.
- Kris-Etherton PM, Dietschy J. Design criteria for studies examining individual fatty acid effects on cardiovascular disease risk factors: human and animal studies. *American Journal of Clinical Nutrition* 1997; 65:1590S-1596S.
- Lichtenstein AH, Russell RM. Essential Nutrients: Food or Supplements? *Journal of American Medical Association* 2005; 294:351-358.
- Milner JA. Diet and Cancer: Facts and Controversies. *Nutrition and Cancer* 2006; 56: 216-224.
- National Cancer Institute, Dictionary of Cancer Terms, **http://www.cancer.gov/dictionary (http://www.cancer.gov/dictionary)**
- National Research Council. Diet and Health: Implications for Reducing Chronic Disease Risk. National Academy Press, Washington, DC, 1989.
- Omenn, GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, Keogh JP, Meyskens FL, Valanis B, Williams JH, Barnhart S, Hammer S. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *New England Journal of Medicine* 1996; 334:1150-1155.
- Peto R, Doll R, Buckley JD, Sporn MB. Can dietary beta-carotene materially reduce human cancer rates? *Nature* 1981; 290:201-208.
- Sempos CT, Liu K, Earnst ND. Food and nutrient exposures: what to consider when evaluating epidemiologic data. *American Journal of Clinical Nutrition* 1999; 69:1330S-1338S.
- Torun B. Protein-energy malnutrition. In: Modern Nutrition in Health and Disease. Williams and Williams, New York, 2006.
- Spilker B. Guide to Clinical Studies. Raven Press, New York, 1991.
- Subar AF, Thompson FE, Kipnis V, Midthune D, Hurwitz P, McNutt S, McIntosh A, Rosenfeld S. Comparative validation of the Block, Willett, and National Cancer Institute Food Frequency Questionnaires, *American Journal of Epidemiology* 2001; 154: 1089-1099.
- Szklo M., Nieto FJ. Epidemiology Beyond the Basics, Aspen Publishing, 2000.

- Willett W.C. Overview of nutritional epidemiology. Nutritional Epidemiology, Oxford University Press, Oxford. 1990.
- Willett W.C. Issues in analysis and presentation of dietary data. In: Nutritional Epidemiology, Second Edition, Oxford University Press, Oxford, 1998.
- Wilson E.B. An Introduction to Scientific Research, General Publishing Company, Toronto, 1990.

back to top

(1) This guidance has been prepared by the Office of Nutrition, Labeling, and Dietary Supplements in the Center for Food Safety and Applied Nutrition at the U.S. Food and Drug Administration.

(2) For brevity, "disease" will be used as shorthand for "disease or health-related condition". "Disease or health-related condition" is defined as damage to an organ, part, structure, or system of the body such that it does not function properly (e.g., cardiovascular disease), or a state of health leading to such dysfunctioning (e.g., hypertension). 21 CFR 101.14(a)(5).

(3) This new guidance document replaces FDA's guidance entitled "Guidance for Industry and FDA: Interim Evidence-based Ranking System for Scientific Data," which addressed the scientific review of qualified health claims. Although the interim evidence-based ranking system guidance included a section on ranking the strength of the scientific evidence, this new guidance document does not include such a section because studies are being conducted on the consumer's understanding of various possible ranking systems that could be used to describe the strength of the evidence for a health claim. FDA intends to reexamine its ranking systems and issue appropriate guidance once these studies are completed. In addition, this guidance document replaces FDA's guidance entitled "Guidance for Industry: Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements."

(4) In 1997, Congress enacted the Food and Drug Administration Modernization Act, which established an alternative authorization procedure for health claims based on authoritative statements of certain federal scientific bodies or the National Academy of Sciences. This guidance document does not address that alternative procedure.

(5) See guidance (Attachment A) entitled "Guidance for Industry and FDA: Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements," July 10, 2003 (http://www.cfsan.fda.gov/~dms/hclmgui3.html)

(6) See 21 U.S.C. 321(ff)(1).

(7) "Nutritive value" is defined in 21 CFR 101.14(a)(3) as value in sustaining human existence by such processes as promoting growth, replacing loss of essential nutrients, or providing energy.

(8) Confounders are factors that are associated with both the disease in question and the intervention, and that if not controlled for, prevent an investigator from being able to conclude that an outcome was caused by an intervention.

(9) Free-living populations represent those who consume diets and have lifestyles (e.g., smoking, drinking, and exercise) of their own choice.

(10) Biomarkers of intake are measurements of the substance itself or a metabolite of the substance in biological samples (e.g., serum selenium) that have been validated to confirm that they reflect the intake of that substance.

(11) Bias is the systematic error that may result in flaws from subject selection (selection bias) or exposure and disease outcome measurements (information bias) (Szklo and Nieto, 2000).

EXHIBIT “D”

Gynecologic Oncology xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Review

Coffee and caffeine intake and breast cancer risk: An updated dose–response meta-analysis of 37 published studies

Wenjie Jiang *, Yili Wu, Xiubo Jiang

Department of Epidemiology and Health Statistics, the Medical College of Qingdao University, Shandong, Qingdao 266021, Dongzhou Road, No. 38, PR China

HIGHLIGHTS

- Coffee and caffeine might be weakly associated with breast cancer risk for postmenopausal women.
- A strong and significant association was found for BRCA1 mutation carriers.

ARTICLE INFO

Article history:
Received 1 February 2013
Accepted 17 March 2013
Available online xxxx

Keywords:
Coffee
Caffeine
Breast cancer
Dose–response meta-analysis

ABSTRACT

Objective. We conducted an updated meta-analysis to summarize the evidence from published studies regarding the association of coffee and caffeine intake with breast cancer risk.

Methods. Pertinent studies were identified by a search of PubMed and by reviewing the reference lists of retrieved articles. The fixed or random effect model was used based on heterogeneity test. The dose–response relationship was assessed by restricted cubic spline model and multivariate random-effect meta-regression.

Results. 37 published articles, involving 59,018 breast cancer cases and 966,263 participants, were included in the meta-analysis. No significant association was found between breast cancer risk and coffee (RR = 0.97, $P = 0.09$), decaffeinated coffee (RR = 0.98, $P = 0.55$) and caffeine (RR = 0.99, $P = 0.73$), respectively. And the association was still not significant when combining coffee and caffeine (coffee/caffeine) (RR = 0.97, $P = 0.09$). However, an inverse association of coffee/caffeine with breast cancer risk was found for postmenopausal women (RR = 0.94, $P = 0.02$), and a strong and significant association of coffee with breast cancer risk was found for BRCA1 mutation carriers (RR = 0.69, $P < 0.01$). A linear dose–response relationship was found for breast cancer risk with coffee and caffeine, and the risk of breast cancer decreased by 2% ($P = 0.05$) for every 2 cups/day increment in coffee intake, and 1% ($P = 0.52$) for every 200 mg/day increment in caffeine intake, respectively.

Conclusions. Findings from this meta-analysis suggested that coffee/caffeine might be weakly associated with breast cancer risk for postmenopausal women, and the association for BRCA1 mutation carriers deserves further investigation.

Contents

* Corresponding author. Fax: +86 532 83801449.
E-mail addresses: jiangwjqd@yahoo.com.cn (W. Jiang), wuylqd@126.com (Y. Wu), jiangxbqd@126.com (X. Jiang).

0090-8258/$ – see front matter © 2013 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.ygyno.2013.03.014

1. Introduction

Breast cancer is the one of the most frequently diagnosed cancer in women, and ranks second as a cause of cancer death in women (after lung cancer) [1]. An estimated 226,870 new cases of invasive breast cancer, 63,300 new cases of in situ breast cancer and 39,510 breast cancer deaths are expected among women in the US during 2012, and the breast cancer incidence rates are stable since 2004 [1]. Coffee is one of the most popular beverages in the world, and the latest coffee trade statistics estimated that world coffee export amounted to about 6.76 billion kg in 2011/2012 [2]. The association between coffee intake and breast cancer risk has been investigated since the early 1970s [3], and many epidemiologic studies have been published on coffee or caffeine intake and breast cancer risk. However, according to the World Cancer Research Fund/American Institute for Cancer Research in 2008, the result was still inconclusive on coffee intake and breast cancer risk for both premenopausal and postmenopausal women [4]. A meta-analysis is available on coffee intake with breast cancer risk [5]. 10 studies (8 cohort studies [6–13] and 2 case–control studies [14,15]) were published thereafter, and we additionally identified10 studies (1 cohort [16] and 9 case–control studies [17–25]) that were published before the meta-analysis. The association of caffeine intake with breast cancer risk is not summarized, and the association of coffee intake with breast cancer risk by menopausal status, body mass index (BMI), estrogen receptor (ER) and progesterone receptor (PR) status, breast cancer stage, and adjustment for important clinical and lifestyle factors is still unknown. Besides, the dose–response relationship, which is essential for proving causality, is also unknown. In addition, categories of coffee and caffeine intake levels differed between studies, which might complicate the interpretation of the pooled results across study populations with different categories. In this respect, a dose–response meta-analysis with restricted cubic spline functions provides a solution to the problem. Therefore, we conducted an updated dose–response meta-analysis to explore the above-mentioned issues in this study.

2. Methods

2.1. Literature search and selection

We performed a literature search up to Dec 2012 using PubMed database with the key words coffee or caffeine combined with breast cancer without restrictions. Furthermore, the reference lists of retrieved articles were scrutinized to identify additional relevant studies.

Two investigators independently reviewed the identified studies, and studies were included if they met the following criteria: (1) the study was conducted in humans; (2) the exposure of interest was coffee or caffeine; (3) the outcome of interest was breast cancer; and (4) relative risk (RR) with 95% confidence interval (CI) was provided (we presented all results with RR for simplicity). For dose–response analysis, the study had to report RR (95% CI) for at least 3 quantitative categories of coffee or caffeine intake. Besides, the number of cases and participants or person-years for each category of coffee or caffeine intake must be also provided (or data available to calculate them). If data were duplicated in more than one study, we included the study with the largest number of cases.

2.2. Data extraction

The following data were extracted from each study by two investigators: the first author's last name, publication year, the name of the cohort study, country where the study was conducted, years of follow-up, age, sample size (number of cases and total number of participants), coffee and caffeine intake categories, covariates adjusted for in the multivariable analysis, and the RRs with their 95% CIs for each category of coffee and caffeine intake. We extracted the RRs that reflected the greatest degree of adjustment for potential confounders. For dose–response analysis, the number of cases and participants (person-years) for each category was also extracted. The median or mean level of coffee and caffeine intake for each category was assigned to the corresponding RR for every study. If the upper boundary of the highest category was not provided, we assumed that the boundary had the same amplitude as the adjacent category [26].

2.3. Statistical analysis

Pooled measure was calculated as the inverse variance-weighted mean of the logarithm of RR (95% CI) of breast cancer for the highest versus lowest category of coffee and caffeine, respectively. The I^2 of Higgins and Thompson was used to assess heterogeneity [27]. I^2 is the proportion of total variation contributed by between-study variation, and I^2 values of 0, 25, 50, and 75% represent no, low, moderate, and high heterogeneity [27], respectively. If moderate or lower heterogeneity ($I^2 < 50\%$) was found, the fixed effect model (FEM) was used as the pooling method, otherwise, the random effect model (REM) was adopted ($I^2 > 50\%$) that considers both within-study and between-study variations. A sensitivity analysis was performed with one study removed at a time to assess whether the results could have been affected markedly by a single study. Publication bias was evaluated using the Egger regression asymmetry test. Subgroup analysis was performed by study design (cohort study or case–control study), follow-up duration for cohort study (<10 years or >10 years), source of controls for case–control study (population-based or hospital-based), menopausal status (premenopausal or postmenopausal), ER and PR status (ER+PR+, ER+PR−, ER−PR+ or ER−PR−), BMI (<25 kg/m^2 or >25 kg/m^2), breast cancer stage (in situ or invasive) and country where the study was conducted (USA, Europe or Asia). Besides, subgroup analysis was also performed by adjustment (yes or no) for smoking and/or alcohol, BMI, total energy intake, physical activity, oral contraceptive use, postmenopausal hormone replacement therapy use, family history of breast cancer and history of benign breast disease.

For dose–response analysis, a two-stage random-effects dose–response meta-analysis [28] was performed to compute the trend from the correlated log RR estimates across levels of coffee and caffeine, respectively, taking into account the between-study heterogeneity. In the first stage, a restricted cubic spline model with three knots at the 25th, 50th, and 75th percentiles [29] of the levels of coffee and caffeine, was estimated using generalized least square regression taking

Please cite this article as: Jiang W, et al, Coffee and caffeine intake and breast cancer risk: An updated dose–response meta-analysis of 37 published studies, Gynecol Oncol (2013), http://dx.doi.org/10.1016/j.ygyno.2013.03.014

into account the correlation within each set of published RRs. Then the study-specific estimates were combined using the restricted maximum likelihood method in a multivariate random-effects meta-analysis [30]. A *P* value for nonlinearity was calculated by testing the null hypothesis that the coefficient of the second spline is equal to 0 [29]. All statistical analyses were performed with STATA version 12.0 (Stata Corporation, College Station, TX, USA). All reported probabilities (*P* values) were two-sided with $P \leq 0.05$ considered statistically significant.

3. Results

3.1. Literature search and study characteristics

The search strategy identified 239 articles, of which 195 articles were excluded after review of the title or abstract (Fig. 1). 44 full-text articles were reviewed. We further excluded 4 articles that did not provide the independent result on coffee and breast cancer, and 3 articles were also excluded because RR and/or 95%CI were not provided. The remaining 37 studies [6–25,31–47] were included in this meta-analysis. 1 study (providing the result for coffee) [7] was a duplicate report from the same population of a previous study (providing the result for coffee and caffeine) [40], thus we included the result for coffee from the recent study [7] because of larger number of cases included. The detailed characteristics of the 37 studies are shown in Table 1.

Among the 37 studies, 28 studies provided the result for coffee [7–9,11,13–23,25,31,32,34–36,39,41–44,46,47], and 6 studies [6,10,12,24,37,45] provided the result for coffee and caffeine separately, and 3 studies [33,38,40] provided the result for caffeine. Because the association of breast cancer risk with coffee was similar with that of breast cancer risk with caffeine in the 6 studies, and the combined result of breast cancer risk with coffee was also similar with that of breast cancer risk with caffeine in this meta-analysis, thus we combined coffee with caffeine (coffee/caffeine) to increase the statistical power in subgroup analysis. 20 studies [14,15,17–25,31–34,38,41,43,46,47] were case–control designs and the remaining 17 studies were cohort designs. 3 studies [22,23,25] examined the association of coffee intake with breast cancer among BRCA1 mutation carriers.

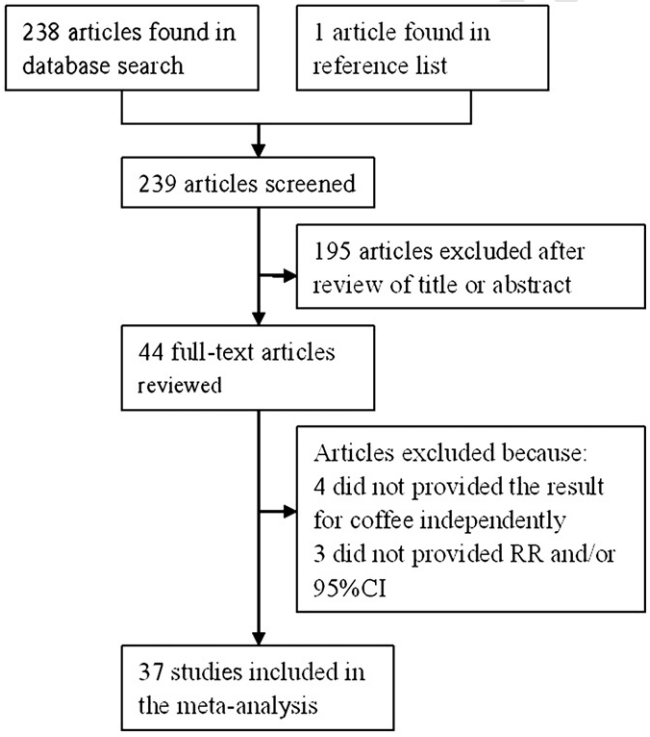

Fig. 1. Selection of studies for inclusion in this meta-analysis.

3.2. Quantitative synthesis

The results are summarized in Table 2.

3.2.1. Overall association of coffee and caffeine with breast cancer risk

Compared to the lowest category, the combined RR (95% CI) of breast cancer for the highest category was 0.99 (0.94–1.04) for caffeine, 0.97 (0.93–1.00) for coffee (Fig. 2) and 0.97 (0.94–1.01) for coffee/caffeine, respectively. 12 studies [6,10,13,18–20,23,32,41,43,45,47] provided the result for decaffeinated coffee, and the RR (95% CI) of breast cancer was 0.98 (0.92 − 1.05) for the highest category versus the lowest category of decaffeinated coffee. The age-adjusted RR (95% CI) of breast cancer was 0.96 (0.92–1.01) for coffee/caffeine [7,13,15,16,24,32,35,37,44,45]. Moderate or lower between-study heterogeneity ($I^2 < 50\%$) was found in all analyses.

3.2.2. Subgroup analysis by study design

An inverse but not significant association was found for both cohort studies (RR = 0.98, 95%CI = 0.95–1.02) and case–control studies (RR = 0.94, 95%CI = 0.89 − 1.00). For cohort studies, similar results were found between studies with the follow-up duration >10 years (RR = 0.99, 95%CI = 0.94–1.04) [6–8,10–12,16,35,36,39,40,45] and <10 years (RR = 0.98, 95%CI = 0.91–1.05) [9,13,37,42,44]. For case–control studies, the association was still not significant for population-based case–control studies (RR = 0.92, 95%CI = 0.84–1.01) [14,15,18,19,21,31,33,34,38,41] and hospital-based case–control studies (RR = 0.96, 95%CI = 0.89–1.05) [17,20,22–25,32,43,46,47], respectively. Moderate or lower between-study heterogeneity ($I^2 < 50\%$) was found in all analyses.

3.2.3. Subgroup analysis by population subgroups

The negative association of coffee/caffeine intake with breast cancer was consistent across different population subgroups by location where the study was conducted (America [6,8,10,13,16,18,19,32,37,41,43,45], Europe [7,9,11,12,15,17,20–22,34–36,38,40,44,46,47], or Asia [24,31,39,42]), BMI (<25 kg/m^2 [6,9,40,45]or >25 kg/m^2 [6,9,40,45]), ER and PR status (ER+PR+ [6,7,10,12,13,45], ER+PR− [6,7,12,13], ER−PR+ [12,13] or ER−PR− [6,7,10,12,13,45]), and breast cancer stage (invasive [6–9,12,13,15,40,45] or in situ [13]). In the subgroup analysis by menopausal status, the association was not significant for premenopausal women [6,8,10,14,21,33,38,40,43,45], but a significant association was found for postmenopausal women (RR = 0.94, 95%CI = 0.8–0.99, $P = 0.02$) [6,10,13–15,21,33,37,40,43,45]. A strong and significant association was found between coffee intake and breast cancer risk among BRCA1 mutation carriers (RR = 0.69, 95%CI = 0.53–0.89, $P = 0.005$). Moderate or lower between-study heterogeneity ($I^2 < 50\%$) was found in all analyses.

3.2.4. Subgroup analysis by adjustment for covariates

No significant association was found in stratified analysis by adjustment (yes or no) for the following covariates: smoking and/or alcohol, BMI, energy intake, physical activity, oral contraceptive use, postmenopausal hormone replacement therapy use, family history of breast cancer and history of benign breast disease. Moderate or lower between-study heterogeneity ($I^2 < 50\%$) was found in all analyses.

3.3. Dose–response analysis

3.3.1. Association of coffee intake with breast cancer

Overall, data from 20 studies [6,7,9–15,23,24,32,34,35,37,40,41,43–45] including 41,805 breast cancer cases were used. Linear relationship was found between coffee intake and breast cancer

Table 1
Characteristics of studies included in the meta-analysis on coffee and caffeine intake and breast cancer.

Author, Year [Ref.]	Study design[a], age (years)	Study name Follow-up (years)	Country	Sample size (cases)	Exposure	RR (95%CI) for highest vs. lowest category	Adjustment for covariates[b]
Snowdon et al. 1984 [16]	Cohort, >40	None, 21	USA	23,912 (176)	Coffee	>2 vs. <1 cups/day 0.9 (0.6–1.3)	Age and sex
Lubin et al. 1985 [31]	CC, unclear	–	Israel	1431 (813)	Coffee	≥4 vs. 0 cup/day 0.6 (0.2–0.9)	None
Rosenberg et al. 1985 [32]	CC, 30–69	–	USA	4152 (2651)	Coffee	>5 vs. 0 cup/day 1.2 (0.9–1.6)	Age, race, religion, smoking, age at menarche, age at first pregnancy, parity, menopause status, age at menopause, FHBC, BMI, education, tea, alcohol, location of the hospital, year of interview, number of previous non-obstetric hospitalizations
Katsouyanni et al. 1986 [17]	CC, 54.7/53.7	–	Greece	240 (120)	Coffee	Consumption level (3th vs. 1th) 1.12 (0.48–2.59)	None
La Vecchia et al. 1986 [46]	CC, unclear	–	Italy	1232 (616)	Coffee	≥4 vs. 0 cup/day 1.1 (0.7–1.7)	Age, geographic area, parity, age at first birth, age at menarche and menopause, OC and HRT use, smoking and alcohol
Schairer et al. 1987 [18]	CC, unclear	BCDDP	USA	3392 (1510)	Coffee	≥5 vs. 0 cup/day 1.0 (0.8–1.3)	None
Rohan et al. 1988 [33]	CC, 20–74	–	Australia	902 (451)	Caffeine	390.0 vs. 158.2 mg/day 1.20 (0.79–1.83)	None
Ewertz et al. 1990 [34]	CC, unclear	–	Denmark	2822 (1486)	Coffee	>10 vs. 0 cup/day 0.81 (0.57–1.15)	Age at diagnosis and place of residence
Vatten et al. 1990 [35]	Cohort, 35–51	None, 12	Norway	14,593 (152)	Coffee	≥5 vs. ≤2 cups/day 0.8 (0.5–1.4)	Age
Hoyer et al. 1992 [36]	Cohort, 30–80	Glostrup Population Studies, 26	Denmark	5207 (51)	Coffee	≥7 vs. ≤2 cups/day 1.7 (0.7–4.3)	Social class, age at menarche, menopause status, number of full-term pregnancies, height, weight, BMI, alcohol and smoking
McLaughlin et al. 1992 [19]	CC, 20–79	–	USA	3234 (1617)	Coffee	Drinker vs. nondrinker 0.98 (0.76–1.26)	Age, county of residence, race, menstrual status, age at first live birth, HBBD, FHBC and alcohol
Folsom et al. 1993 [37]	Cohort, 55–69	Iowa Women's Health Study, 5	USA	34,388 (580)	Coffee	≥4 vs. 0 cup/day 1.02 (0.79–1.30) ≥503.8 vs. ≤65.2 mg/day 1.02 (0.78–1.33)	Age, waist/hip ratio, number of live births, age at first live birth, age at menarche, FHBC, Family history × waist/hip ratio, and family history × number of live births
Levi et al. 1993 [20]	CC, 30–75	–	Switzerland	425 (107)	Coffee	Consumption level (3th vs. 1th) 0.98 (0.53–1.79)	None
Smith et al. 1994 [38]	CC, <36	–	UK	1510 (755)	Caffeine	>301 vs. <100 mg/day 0.83 (0.59–1.17)	Age at menarche, nulliparity, age at first full-term pregnancy, breastfeeding, FHBC, OC use, HBBD, alcohol at 18 and smoking
Tavani et al. 1998 [47]	CC, <75	–	Italy	11,488 (5984)	Coffee	≥4 vs. <2 cups/day 0.96 (0.83–1.11)	Study/center, age, education, BMI, smoking, alcohol, age at menarche and menopause, parity and age at first birth, OC use, HRT, HBBD, FHBC
Key et al. 1999 [39]	Cohort, <40– > 80	RERFLS, >14	Japan	34,759 (427)	Coffee	≥5 vs. ≤ 1 times/day 1.19 (0.93–1.52)	Age, calendar period, city, age at time of bombing and radiation dose
Mannisto et al.1999 [21]	CC, 25–75	–	Finland	764 (310)	Coffee	Consumption level (4th vs. 1th) Premenopausal 1.8 (0.8–4.3) Postmenopausal 0.5 (0.3–1.0)	Age, area (rural/urban), age at menarche, age at first full-term pregnancy, OC use, HRT, FHBC, HBBD, education, alcohol, smoking, leisure activity and waist/hip ratio.
Michels et al. 2002 [40]	Cohort, 40–76	Swedish Mammography Cohort, 11	Sweden	59,036 (1271)	Caffeine	308.8 vs. 83.8 g/day 1.04 (0.87–1.24)	Age, family history of breast cancer, height, BMI, education, parity, age at first birth, alcohol and caloric intake
Wu et al. 2003 [41]	CC, 25–74	–	USA	1095 (501)	Coffee	>240 vs. 0 ml/day 0.77 (0.53–1.12)	Age, Asian ethnicity, birthplace, education, age at menarche, pregnancy, current BMI, caloric intake, menopausal status,

							HRT use, intake of soy and dark green vegetables, smoking, alcohol, physical activity, FHBR
Suzuki et al. 2004 [42]	Cohort, 40–64	None, 8	Japan	35,004 (222)	Coffee	≥1 vs. 0 cup/day 0.81 (0.55–1.18)	Age, types of health insurance, age at menarche, menopausal status, age at first birth, parity, FHBC, smoking, alcohol, BMI and tea
Baker et al. 2006 [43]	CC, 21–94	–	USA	3827 (1932)	Coffee	>4 vs. 0 cup/day Premenopausal 0.62 (0.39–0.98) Postmenopausal 0.99 (0.79–1.23)	Age, residence, and age at birth of first child Age and residence
Gronwald et al. 2006 [22]	CC, 43.9/36.4	–	Poland	696 (348)	Coffee	Drinker vs. nondrinker 0.8 (0.5–1.1)	Year of birth, age at diagnosis, age at menarche, parity, smoking, breast-feeding and OC use
Hivonen et al. 2006 [44]	Cohort, 35–60	SU.VI.MAX Study, 6.6	Finland	4396 (95)	Coffee	≥253 vs. <111 ml/day 1.10 (0.66–1.84)	Age, smoking, number of children, OC use, FHBC and menopausal status
Nkondjock et al. 2006 [23]	CC, <64	–	Four countries	1690 (845)	Coffee	≥6 vs. 0 cup/day 0.51 (0.26–0.98)	Parity, smoking, OC use, alcohol and BMI at age 30
Hirose et al. 2007 [24]	CC, 40–79	HERPACC study	Japan	14,547 (2122)	Coffee Caffeine	>3 vs. 0 cup/day 1.04 (0.85–1.28) >270 vs. ≤120 mg/day 1.03 (0.89–1.20)	Age, year, motivation for consultation, parity, age at first delivery, smoking, alcohol, type of breakfast, fondness of salty and fatty foods, fruit, vegetable, beef, fish, carrot, exercise and BMI
Kotsopoulos et al. 2007 [25]	CC, 52.4/43.1	–	Canada	411 (170)	Coffee	Drinker vs. nondrinker 0.61 90.38–0.97)	Year of birth, age at menarche, parity and smoking
Ganmaa et al. 2008 [45]	Cohort, 30–55	Nurses' Health Study, 22	USA	85,987 (5272)	Coffee Caffeine	≥6 cups/day vs. <1 cup/month 0.92 (0.82–1.03) 816 vs. 51 mg/day 0.93 (0.85–1.01)	Age, smoking, BMI, physical activity, height, alcohol, FHBC, HBBD, menopausal status, age at menopause, HRT use, age at menarche, weight change after 18 and duration of HRT
Ishitani et al. 2008 [6]	Cohort, >45	Women's Health Study, 10	USA	38,432 (1188)	Coffee Caffeine	≥4 vs. 0 cup/day 1.08 (0.89–1.30) >486.3 vs. ≤68.0 mg/day 1.02 (0.84–1.22)	Age, randomized treatment assignment, BMI, physical activity, energy, alcohol, multivitamin use, age at menopause, age at menarche, age at first pregnancy lasting ≥6 months, number of pregnancies lasting ≥6 months, menopausal status, HRT use, prior hysterectomy, prior bilateral oophorectomy, smoking, FHBC and HBBD
Bissonauth et al. 2009 [14]	CC, <35– > 65	–	Canada	560 (280)	Coffee	>8 vs. ≤2 cups/day 1.4 (1.09–2.24)	Age, education, physical activity, smoking, coffee and energy
Larsson et al. 2009 [7]	Cohort, 40–76	Swedish Mammography Cohort, 17.4	Sweden	61,433 (2952)	Coffee	≥4 vs. <1 cups/day 1.02 (0.87–1.20)	Age, education, BMI, height, parity, age at first birth, age at menarche, age at menopause, OC use, HRT use, FHBC, energy, alcohol and tea
Wilson et al. 2009 [8]	Cohort, 25–42	Nurses' Health Study II, 14	USA	90,628 (1179)	Coffee	consumption level (5th vs. 1th) 0.92 (0.77–1.11)	BMI, height, OC use, parity and age at first birth, age at menarche, FHBC, HBBD, smoking, physical activity, animal fat, glycemic load, alcohol and energy
Bhoo et al. 2010 [9]	Cohort, 20–70	EPIC-NL Cohort, 9.6	Netherlands	27,323 (681)	Coffee	>5 vs. 0 cup/day 0.94 (0.72–1.24)	Age, smoking, education, BMI, alcohol, energy, saturated fat, fiber, tea, physical activity, OC use, presence of hypercholesterolemia, FHBC, age at menarche and parity
Boggs et al. 2010 [10]	Cohort, 21–69	Black Women's Health Study, 12	USA	52,062 (1268)	Coffee Caffeine	≥4 vs. <1 cups/day 1.03 (0.77–1.39) ≥209 vs. <16 mg/day 1.04 (0.87–1.24)	Age, energy, age at menarche, BMI at age 18, FHBC, education, geographic region, parity, age at first birth, OC use, menopausal status, age at menopause, HRT use, vigorous activity, smoking and alcohol
Nilsson et al. 2010 [11]	Cohort, >30	Vasterbotten Intervention Project, 15	Sweden	64,603 (3034)	Coffee	≥4 vs. <1 cups/day 0.92 (0.68–1.25)	Age, sex, BMI, smoking, education, and recreational physical activity

(continued on next page)

Table 1 (*continued*)

Author, Year [Ref.]	Study design[a], age (years)	Study name Follow-up (years)	Country	Sample size (cases)	Exposure	RR (95%CI) for highest vs. lowest category	Adjustment for covariates[b]
Fagherazzi et al. 2011 [12]	Cohort, 40–65	E3N cohort, 11	France	67,703 (2868)	Coffee Caffeine	>3 vs. 0 cup/day 1.02 (0.90–1.16) 351 vs. 48 mg/day 1.02 (0.93–1.13)	Age, energy, OC use, age at menarche, age at menopause, number of children, age at first pregnancy, FHBC, education, HRT use, HBBD, menopausal status and BMI
Li et al. 2011 [15]	CC, 50–74	– MARIE	Sweden Germany	5929 (2818) 8046 (2651)	Coffee Coffee	>5 vs. ≤1 cups/day 0.84 (0.66–1.06) >5 vs. ≤1 cups/day 0.87 (0.71–1.07)	Age, HRT use, smoking, education and alcohol
Gierach et al. 2012 [13]	Cohort, 50–71	Health-AARP Diet and Health Study cohort, 5.2/9.8	USA	198,404 (9915)	Coffee	Coffee: >4 vs. 0 cup/day 0.98 (0.91–1.07)	Age, race/ethnicity, education, BMI, smoking, alcohol, proportion of total energy from fat, age at first live birth, HRT use, history of breast biopsy and FHBC

[a] CC: case–control study.
[b] BMI: body mass index, OC: oral contraceptive, HRT: hormone replacement therapy, FHBC: family history of breast cancer, HBBD: history of benign breast disease.

risk (P for nonlinearity = 0.49), and the RR (95% CI) of breast cancer was 1.00 (0.98–1.01), 0.99 (0.96–1.02), 0.98 (0.95–1.01), 0.97 (0.94–1.01), 0.95 (0.92–1.00), 0.94 (0.90–0.99), 0.93 (0.88–0.98) and 0.92 (0.85–0.98) for 1, 2, 3, 4, 5, 6, 7 and 8 cups/day of coffee intake, respectively. The risk of breast cancer decreased by 2% (RR = 0.98, 95%CI = 0.96–1.00, P = 0.053) for every 2 cups/day increment in coffee intake.

For case–control study, data from 8 studies [14,15,23,24,32,34,41,43] including 15,195 breast cancer cases were used. Linear relationship was found between coffee intake and breast cancer risk (P for nonlinearity = 0.18), and the RR (95% CI) of breast cancer was 1.01 (0.98–1.04), 1.01 (0.95–1.07), 1.00 (0.94–1.06), 0.97 (0.92–1.04), 0.95 (0.89–1.01), 0.93 (0.86–1.00), 0.90 (0.82–0.99) and 0.88 (0.79–0.99) for 1, 2, 3, 4, 5, 6, 7 and 8 cups/day of coffee intake, respectively. The risk of breast cancer decreased by 3% (RR = 0.97, 95%CI = 0.93–1.02, P = 0.21) for every 2 cups/day increment in coffee intake.

For cohort study, data from 12 studies including 26,610 breast cancer cases were used. Linear relationship was found between coffee intake and breast cancer risk (P for nonlinearity = 0.72), and the RR (95% CI) of breast cancer was 0.99 (0.97–1.01), 0.98 (0.94–1.02), 0.97 (0.94–1.01), 0.97 (0.93–1.00), 0.96 (0.92–1.01), 0.96 (0.91–1.01) and 0.95 (0.89–1.02) for 1, 2, 3, 4, 5, 6 and 7 cups/day of coffee intake, respectively (Fig. 3). The risk of breast cancer decreased by 2% (RR = 0.98, 95%CI = 0.97–1.00, P = 0.08) for every 2 cups/day increment in coffee intake.

3.3.2. Association of caffeine intake with breast cancer

Data from 7 studies [6,10,12,24,37,38,45] including 14,020 breast cancer cases were used. Linear relationship was found between caffeine intake and breast cancer risk (P for nonlinearity = 0.61), and the RR (95% CI) of breast cancer was 1.00 (0.98–1.03), 1.00 (0.96–1.05), 1.00 (0.95–1.04), 0.99 (0.95–1.03), 0.98 (0.94–1.03), 0.98 (0.93–1.03), 0.97 (0.92–1.03) and 0.96 (0.90–1.03) for 100, 200, 300, 400, 500, 600, 700 and 800 mg/day of caffeine intake, respectively (Fig. 4). The risk of breast cancer decreased by 1% (RR = 0.99, 95%CI = 0.98–1.01, P = 0.52) for every 200 mg/day increment in caffeine intake. Considering the limited number of studies included, stratified analysis by study design (case–control and cohort) was not performed.

3.4. Sensitivity analysis and publication bias

Sensitivity analysis showed that no individual study had excessive influence on the pooled effect between breast risk and coffee and caffeine intake, respectively. Egger test showed no evidence of significant publication bias for the analysis between breast cancer risk and coffee (P = 0.23) and caffeine (P = 0.35), respectively.

4. Discussion

Findings from this meta-analysis suggested that coffee/caffeine might be weakly associated with breast cancer risk for postmenopausal women, and a strong and significant association of coffee with breast cancer risk was found among BRCA1 mutation carriers. A linear but not significant dose–response relationship was found between breast cancer risk and coffee and caffeine intake, respectively.

Coffee is a complex chemical mixture that contains many compounds including caffeine, acrylamide, various polyphenols, etc. which can play a dual role as both a carcinogen and a chemo-preventive agent. Animal tests showed that caffeine can both promote and suppress mammary tumors [48]. And acrylamide was also shown to increase breast cancer risk [8]. Experimental studies suggested that polyphenols, like chlorogenic acid and caffeic acid and lignans could interfere at the initiation, promotion and progression of cancer [49]. Furthermore, previous studies suggested that coffee and caffeine were inversely correlated with sex hormones (testosterone and estradiol)

Please cite this article as: Jiang W, et al, Coffee and caffeine intake and breast cancer risk: An updated dose–response meta-analysis of 37 published studies, Gynecol Oncol (2013), http://dx.doi.org/10.1016/j.ygyno.2013.03.014

Table 2
Pooled measures on the relation of coffee and caffeine to breast cancer.

	Fixed effect model (FEM)	Random effect model (REM)	P^a	I^2 (%)	Number of studies	Number of breast cancer cases
Caffeine	0.99 (0.94–1.04)	0.99 (0.94–1.04)	0.73	0.00	9	15,775
Coffee	0.97 (0.93–1.00)	0.97 (0.92–1.01)	0.09	14.2	34	56,541
Decaffeinated coffee	0.98 (0.92–1.05)	0.97 (0.89–1.06)	0.55	29.7	12	31,790
Caffeine/coffee	0.97 (0.94–1.01)	0.97 (0.93–1.01)	0.09	12.3	37	59,018
Age-adjusted RR	0.96 (0.92–1.01)	0.95 (0.88–1.03)	0.15	42.6	10	29,384
BRCA1 mutation carriers	0.69 (0.53–0.89)	0.69 (0.53–0.89)	0.01	0.00	3	1363
Study design						
Cohort study	0.98 (0.95–1.02)	0.98 (0.95–1.02)	0.44	0.00	17	30,931
Case–control study	0.94 (0.89–1.00)	0.93 (0.85–1.01)	0.06	34.0	20	28,087
Follow-up duration for cohort studies						
>10 years	0.99 (0.94–1.04)	0.99 (0.94–1.04)	0.62	0.00	12	19,438
<10 years	0.98 (0.91–1.05)	0.98 (0.91–1.05)	0.50	0.00	5	11,493
Source of controls for case–control study						
Population-based	0.92 (0.84–1.01)	0.92 (0.81–1.04)	0.09	37.5	10	13,192
Hospital-based	0.96 (0.89–1.05)	0.94 (0.84–1.06)	0.13	33.7	10	14,895
Menopausal status						
Premenopausal	0.97 (0.87–1.07)	0.97 (0.86–1.09)	0.50	10.1	10	4842
Postmenopausal	0.94 (0.89–0.99)	0.94 (0.89–1.00)	0.02	9.10	11	24,188
Country						
USA	0.97 (0.92–1.01)	0.97 (0.92–1.01)	0.14	0.00	12	27,789
Asia	1.03 (0.91–1.16)	1.00 (0.83–1.21)	0.66	37.9	4	3184
Europe	0.97 (0.92–1.02)	0.97 (0.92–1.02)	0.24	0.00	17	26,299
Body mass index (BMI)						
<25 kg/m^2	1.01 (0.90–1.12)	1.01 (0.90–1.12)	0.91	0.00	4	4372
>25 kg/m^2	0.92 (0.82–1.04)	0.92 (0.82–1.04)	0.18	0.00	4	4029
Estrogen receptor (ER) and progesterone receptor (PR) status (positive: +, negative: –)						
ER + PR+	0.96 (0.89–1.04)	0.96 (0.88–1.06)	0.28	16.1	6	8094
ER + PR–	1.05 (0.88–1.26)	1.05 (0.88–1.26)	0.59	0.00	4	1449
ER–PR+	0.70 (0.43–1.15)	0.70 (0.43–1.15)	0.16	0.00	2	155
ER–PR–	0.95 (0.83–1.09)	0.97 (0.83–1.13)	0.48	15.8	6	2214
Breast cancer stage						
Invasive	0.97 (0.92–1.01)	0.97 (0.92–1.01)	0.15	0.00	9	27,828
In situ	1.02 (0.85–1.24)	1.02 (0.85–1.24)	–	–	1	1892
Adjustment for smoking and/or alcohol						
No	1.00 (0.93–1.07)	1.00 (0.93–1.07)	0.98	0.00	12	10,222
Yes	0.96 (0.93–1.00)	0.96 (0.92–1.01)	0.06	20.0	25	48,796
Adjustment for BMI						
No	0.95 (0.88–1.01)	0.94 (0.86–1.03)	0.12	26.0	22	17,065
Yes	0.98 (0.94–1.02)	0.98 (0.94–1.02)	0.29	0.00	15	41,953
Adjustment for energy intake						
No	0.94 (0.90–0.99)	0.94 (0.89–1.00)	0.02	16.1	27	36,915
Yes	1.00 (0.96–1.05)	1.00 (0.96–1.05)	0.97	0.00	10	22,103
Adjustment for physical activity						
No	0.98 (0.94–1.02)	0.97 (0.93–1.02)	0.24	4.90	27	43,183
Yes	0.97 (0.91–1.02)	0.97 (0.90–1.06)	0.22	33.1	10	15,835
Adjustment for oral contraceptive (OC) use						
No	0.97 (0.93–1.01)	0.97 (0.92–1.02)	0.12	11.9	25	41,117
Yes	0.98 (0.93–1.04)	0.97 (0.90–1.04)	0.50	19.2	12	17,901
Adjustment for postmenopausal hormone replacement therapy (HRT)[b]						
No	0.99 (0.93–1.05)	0.98 (0.91–1.05)	0.75	16.6	24	36,343
Yes	0.97 (0.93–1.01)	0.97 (0.92–1.02)	0.13	15.3	11	20,740
Adjustment for family history of breast cancer (FHBC)						
No	0.97 (0.91–1.03)	0.95 (0.88–1.03)	0.27	26.6	20	20,980
Yes	0.98 (0.94–1.01)	0.98 (0.94–1.01)	0.20	0.00	17	38,038
Adjustment for history of benign breast disease (HBBD)						
No	0.97 (0.94–1.02)	0.98 (0.93–1.03)	0.34	12.3	29	39,845
Yes	0.96 (0.91–1.01)	0.96 (0.90–1.02)	0.14	20.0	8	19,173

[a] P value for significance test of RR in FEM because all $I^2 < 50\%$.
[b] 2 studies with premenopausal women only were excluded in this analysis.

[50,51] and positively associated with sex hormone-binding globulin (SHBG) levels among postmenopausal women [50,52]. And increased risks of breast cancer were found associated with elevated serum concentrations of testosterone and estradiol among postmenopausal women [53–55], while high levels of SHBG was found associated with decreased risk of breast cancer among postmenopausal women [53]. This might partially explain the observed association among postmenopausal women in this meta-analysis. BRCA1 is a well-indentified gene involved in breast cancer, and the cumulative risk of breast cancer was estimated to be 54% by age 60 years, and 85% by age 70 among BRCA1 mutation carriers [56]. Thus exploring the effect of coffee on breast cancer among BRCA1 mutation carriers also received much attention [22,23,25]. However, the mechanism for BRCA1 mutation interacting with coffee/caffeine for breast cancer risk is still unclear. The previous study indicated that majority of BRCA1-associated breast cancers are estrogen-receptor negative (ER−) [57], and protection was also somewhat stronger for ER− breast cancer in this meta-analysis, especially for ER−PR+ breast cancer (RR = 0.70). However,

Please cite this article as: Jiang W, et al, Coffee and caffeine intake and breast cancer risk: An updated dose–response meta-analysis of 37 published studies, Gynecol Oncol (2013), http://dx.doi.org/10.1016/j.ygyno.2013.03.014

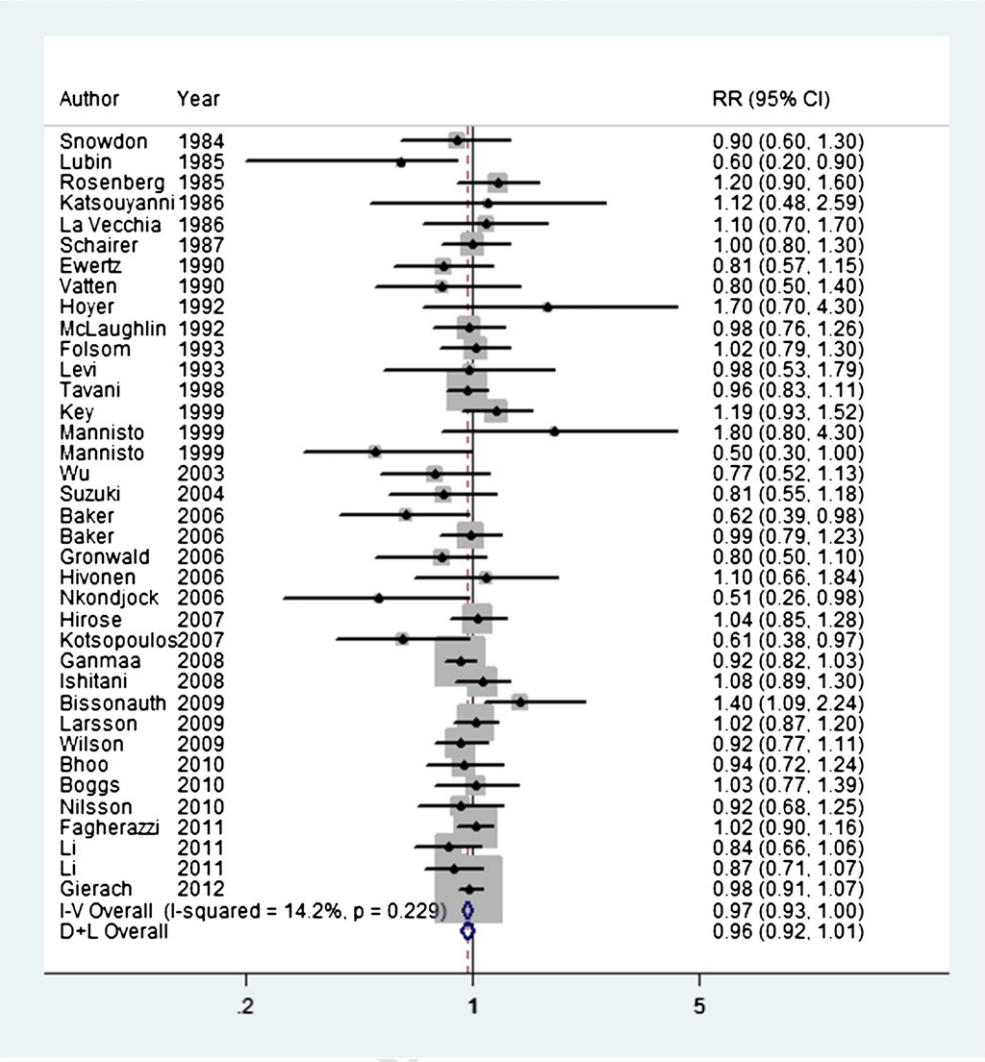

Fig. 2. The multivariate-adjusted risk of breast cancer for the highest vs. lowest categories of coffee intake. The size of gray box is positively proportional to the weight assigned to each study, which is inversely proportional to the standard error of the RR, and horizontal lines represent the 95%confidence intervals. D + L denotes random effect model (REM), I–V denotes fixed effect model (FEM).

only 2 results were included in this meta-analysis on coffee/caffeine and ER−PR+ breast cancer, which needs to be confirmed in the further studies.

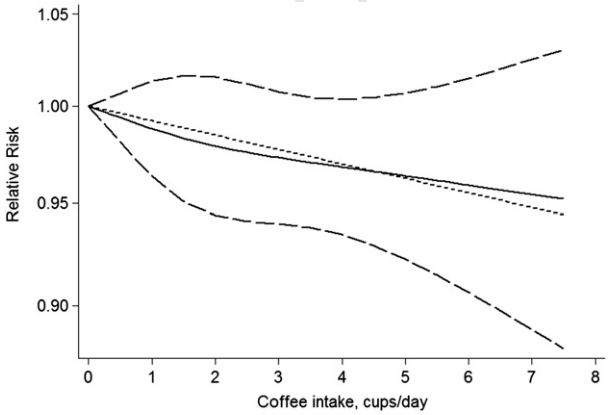

Fig. 3. The dose–response analysis between coffee intake and breast cancer risk in cohort studies with restricted cubic splines in a multivariate random-effects dose–response model. The solid line and the long dash line represent the estimated relative risk and its 95% confidence interval. Short dash line represents the linear relationship.

Observational studies cannot prove causality. However, results of our meta-analysis do not support an obvious causation overall according to the Hill criteria [58]. (1) Strength: the magnitude of this association is negligible overall; (2) Consistency: negative association was found in almost all stratified analyses and low between-study heterogeneity was found in most subgroup analysis; (3) Temporality: negative association from the prospective studies does not consist of an appropriate temporal relationship, in which the exposure precedes breast cancer incidence; (4) Plausibility and coherence: coffee and caffeine can both promote and suppress mammary tumors. (5) Biological gradient: the linear but not significant dose–response relationship does not meet an obviously biological gradient. Although marginally significant association was found for coffee consumers of ≥6 cups/day overall, it has little public health significance, considering the fact that Finnish who consume the most amount of coffee (12 kg per person) in the world do not consume that much of coffee (Current Worldwide Annual Coffee Consumption per capita around 2009, http://chartsbin.com/view/581, accessed 1/10/2013).

A major strength of this study was the large number of participants included, allowing a much greater possibility of reaching reasonable conclusions and conducting subgroup analysis. Dose–response analysis was also performed to better describe the association of breast cancer risk with coffee and caffeine intake. However, there were some limitations in this meta-analysis. First, only 3 studies [22,23,25] were included

Please cite this article as: Jiang W, et al, Coffee and caffeine intake and breast cancer risk: An updated dose–response meta-analysis of 37 published studies, Gynecol Oncol (2013), http://dx.doi.org/10.1016/j.ygyno.2013.03.014

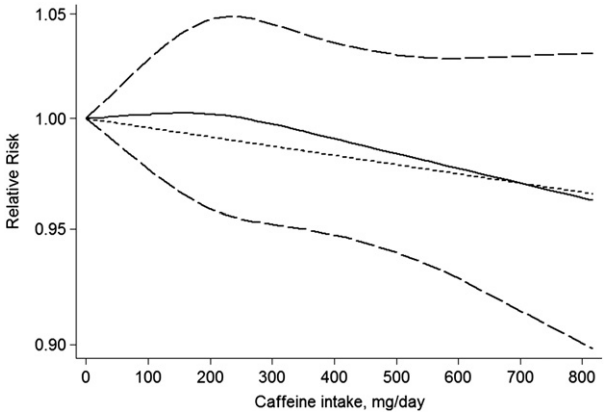

Fig. 4. The dose–response analysis between caffeine intake and breast cancer risk with restricted cubic splines in a multivariate random-effects dose–response model. The solid line and the long dash line represent the estimated relative risk and its 95% confidence interval. Short dash line represents the linear relationship.

for BRCA1 mutation carriers, thus the observed association needs to be confirmed in the further studies. Second, misclassification of coffee consumption was inevitable in the original studies. However, results from validation studies suggested that coffee consumption was assessed with relatively high validity [59]. Third, although we extracted the RRs that reflected the greatest degree of control for potential confounders, but the extent to which they were adjusted varied in the original studies. However, the strength of effect estimates was similar between age-adjusted RR and multivariate-adjusted RR, and similar result was also found by adjustment (yes or no) of selected key covariates. Finally, in a meta-analysis of published studies, it is possible that an observed effect might suffer from publication bias because studies with null results tend not to be published. However, no significant publication bias was detected in this meta-analysis.

In summary, results from this meta-analysis indicated that coffee/caffeine might be weakly associated with breast cancer risk for postmenopausal women, and the association of coffee with breast cancer risk for BRCA1 mutation carriers deserves further investigation.

Conflict of interest statement

None.

References

[1] American Cancer Society. Cancer Facts and Figures 2012. New York (NY): American Cancer Society; 2012.
[2] International Coffee Organization, accessed on 1/6/2013.
[3] Stocks P. Cancer mortality in relation to national consumption of cigarettes, solid fuel, tea and coffee. Br J Cancer 1970;24:215–25.
[4] Norat T, Chan D, Lau T, Vieira R, Thompson T. WCRF/AICR Systematic Literature Review Continuous Update Report. The Associations Between Food, Nutrition and Physical Activity and the Risk of Breast Cancer; 2008.
[5] Tang N, Zhou B, Wang B, Yu R. Coffee consumption and risk of breast cancer: a metaanalysis.Am J Obstet Gynecol 2009;200:290 e291 [299].
[6] Ishitani K, Lin J, Manson JE, Buring JE, Zhang SM. Caffeine consumption and the risk of breast cancer in a large prospective cohort of women. Arch Intern Med 2008;168:2022–31.
[7] Larsson SC, Bergkvist L, Wolk A. Coffee and black tea consumption and risk of breast cancer by estrogen and progesterone receptor status in a Swedish cohort. Cancer Causes Control 2009;20:2039–44.
[8] Wilson KM, Mucci LA, Cho E, Hunter DJ, Chen WY, Willett WC. Dietary acrylamide intake and risk of premenopausal breast cancer. Am J Epidemiol 2009;169:954–61.
[9] Bhoo Pathy N, Peeters P, van Gils C, Beulens JW, van der Graaf Y, Bueno-de-Mesquita B, et al. Coffee and tea intake and risk of breast cancer. Breast Cancer Res Treat 2010;121:461–7.
[10] Boggs DA, Palmer JR, Stampfer MJ, Spiegelman D, Adams-Campbell LL, Rosenberg L. Tea and coffee intake in relation to risk of breast cancer in the Black Women's Health Study. Cancer Causes Control 2010;21:1941–8.
[11] Nilsson LM, Johansson I, Lenner P, Lindahl B, Van Guelpen B. Consumption of filtered and boiled coffee and the risk of incident cancer: a prospective cohort study. Cancer Causes Control 2010;21:1533–44.
[12] Fagherazzi G, Touillaud MS, Boutron-Ruault MC, Clavel-Chapelon F, Romieu I. No association between coffee, tea or caffeine consumption and breast cancer risk in a prospective cohort study. Public Health Nutr 2011;14:1315–20.
[13] Gierach GL, Freedman ND, Andaya A, Hollenbeck AR, Park Y, Schatzkin A, et al. Coffee intake and breast cancer risk in the NIH-AARP diet and health study cohort. Int J Cancer 2012;131:452–60.
[14] Bissonauth V, Shatenstein B, Fafard E, Maugard C, Robidoux A, Narod S, et al. Risk of breast cancer among French–Canadian women, noncarriers of more frequent BRCA1/2 mutations and consumption of total energy, coffee, and alcohol. Breast J 2009;15(Suppl. 1):S63–71.
[15] Li J, Seibold P, Chang-Claude J, Flesch-Janys D, Liu J, Czene K, et al. Coffee consumption modifies risk of estrogen-receptor negative breast cancer. Breast Cancer Res 2011;13:R49.
[16] Snowdon DA, Phillips RL. Coffee consumption and risk of fatal cancers. Am J Public Health 1984;74:820–3.
[17] Katsouyanni K, Trichopoulos D, Boyle P, Xirouchaki E, Trichopoulou A, Lisseos B, et al. Diet and breast cancer: a case–control study in Greece. Int J Cancer 1986;38:815–20.
[18] Schairer C, Brinton LA, Hoover RN. Methylxanthines and breast cancer. Int J Cancer 1987;40:469–73.
[19] McLaughlin CC, Mahoney MC, Nasca PC, Metzger BB, Baptiste MS, Field NA. Breast cancer and methylxanthine consumption. Cancer Causes Control 1992;3:175–8.
[20] Levi F, La Vecchia C, Gulie C, Negri E. Dietary factors and breast cancer risk in Vaud, Switzerland. Nutr Cancer 1993;19:327–35.
[21] Mannisto S, Pietinen P, Virtanen M, Kataja V, Uusitupa M. Diet and the risk of breast cancer in a case-control study: does the threat of disease have an influence on recall bias? J Clin Epidemiol 1999;52:429–39.
[22] Gronwald J, Byrski T, Huzarski T, Cybulski C, Sun P, Tulman A, et al. Influence of selected lifestyle factors on breast and ovarian cancer risk in BRCA1 mutation carriers from Poland. Breast Cancer Res Treat 2006;95:105–9.
[23] Nkondjock A, Ghadirian P, Kotsopoulos J, Lubinski J, Lynch H, Kim-Sing C, et al. Coffee consumption and breast cancer risk among BRCA1 and BRCA2 mutation carriers. Int J Cancer 2006;118:103–7.
[24] Hirose K, Niwa Y, Wakai K, Matsuo K, Nakanishi T, Tajima K. Coffee consumption and the risk of endometrial cancer: evidence from a case–control study of female hormone-related cancers in Japan. Cancer Sci 2007;98:411–5.
[25] Kotsopoulos J, Ghadirian P, El-Sohemy A, Lynch HT, Snyder C, Daly M, et al. The CYP1A2 genotype modifies the association between coffee consumption and breast cancer risk among BRCA1 mutation carriers. Cancer Epidemiol Biomarkers Prev 2007;16:912–6.
[26] Larsson SC, Orsini N. Coffee consumption and risk of stroke: a dose–response meta-analysis of prospective studies. Am J Epidemiol 2011;174:993–1001.
[27] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
[28] Orsini N, Li R, Wolk A, Khudyakov P, Spiegelman D. Meta-analysis for linear and nonlinear dose–response relations: examples, an evaluation of approximations, and software. Am J Epidemiol 2012;175:66–73.
[29] Harrell Jr FE, Lee KL, Pollock BG. Regression models in clinical studies: determining relationships between predictors and response. J Natl Cancer Inst 1988;80:1198–202.
[30] Jackson D, White IR, Thompson SG. Extending DerSimonian and Laird's methodology to perform multivariate random effects meta-analyses. Stat Med 2010;29:1282–97.
[31] Lubin F, Ron E, Wax Y, Modan B. Coffee and methylxanthines and breast cancer: a case–control study. J Natl Cancer Inst 1985;74:569–73.
[32] Rosenberg L, Miller DR, Helmrich SP, Kaufman DW, Schottenfeld D, Stolley PD, et al. Breast cancer and the consumption of coffee. Am J Epidemiol 1985;122:391–9.
[33] Rohan TE, McMichael AJ. Methylxanthines and breast cancer. Int J Cancer 1988;41:390–3.
[34] Ewertz M, Gill C. Dietary factors and breast-cancer risk in Denmark. Int J Cancer 1990;46:779–84.
[35] Vatten LJ, Solvoll K, Loken EB. Coffee consumption and the risk of breast cancer. A prospective study of 14,593 Norwegian women. Br J Cancer 1990;62:267–70.
[36] Hoyer AP, Engholm G. Serum lipids and breast cancer risk: a cohort study of 5,207 Danish women. Cancer Causes Control 1992;3:403–8.
[37] Folsom AR, McKenzie DR, Bisgard KM, Kushi LH, Sellers TA. No association between caffeine intake and postmenopausal breast cancer incidence in the Iowa Women's Health Study. Am J Epidemiol 1993;138:380–3.
[38] Smith SJ, Deacon JM, Chilvers CE. Alcohol, smoking, passive smoking and caffeine in relation to breast cancer risk in young women. UK National Case–Control Study Group. Br J Cancer 1994;70:112–9.
[39] Key TJ, Sharp GB, Appleby PN, Beral V, Goodman MT, Soda M, et al. Soya foods and breast cancer risk: a prospective study in Hiroshima and Nagasaki, Japan. Br J Cancer 1999;81:1248–56.
[40] Michels KB, Holmberg L, Bergkvist L, Wolk A. Coffee, tea, and caffeine consumption and breast cancer incidence in a cohort of Swedish women. Ann Epidemiol 2002;12:21–6.
[41] Wu AH, Yu MC, Tseng CC, Hankin J, Pike MC. Green tea and risk of breast cancer in Asian Americans. Int J Cancer 2003;106:574–9.
[42] Suzuki Y, Tsubono Y, Nakaya N, Koizumi Y, Tsuji I. Green tea and the risk of breast cancer: pooled analysis of two prospective studies in Japan. Br J Cancer 2004;90:1361–3.
[43] Baker JA, Beehler GP, Sawant AC, Jayaprakash V, McCann SE, Moysich KB. Consumption of coffee, but not black tea, is associated with decreased risk of premenopausal breast cancer. J Nutr 2006;136:166–71.

[44] Hirvonen T, Mennen LI, de Bree A, Castetbon K, Galan P, Bertrais S, et al. Consumption of antioxidant-rich beverages and risk for breast cancer in French women. Ann Epidemiol 2006;16:503–8.
[45] Ganmaa D, Willett WC, Li TY, Feskanich D, van Dam RM, Lopez-Garcia E, et al. Coffee, tea, caffeine and risk of breast cancer: a 22-year follow-up. Int J Cancer 2008;122:2071–6.
[46] La Vecchia C, Talamini R, Decarli A, Franceschi S, Parazzini F, Tognoni G. Coffee consumption and the risk of breast cancer. Surgery 1986;100:477–81.
[47] Tavani A, Pregnolato A, La Vecchia C, Favero A, Franceschi S. Coffee consumption and the risk of breast cancer. Eur J Cancer Prev 1998;7:77–82.
[48] Welsch CW, Scieszka KM, Senn ER, DeHoog JV. Caffeine (1,3,7-trimethylxanthine), a temperature promoter of DMBA-induced rat mammary gland carcinogenesis. Int J Cancer 1983;32:479–84.
[49] Ramos S. Cancer chemoprevention and chemotherapy: dietary polyphenols and signalling pathways. Mol Nutr Food Res 2008;52:507–26.
[50] Kotsopoulos J, Eliassen AH, Missmer SA, Hankinson SE, Tworoger SS. Relationship between caffeine intake and plasma sex hormone concentrations in premenopausal and postmenopausal women. Cancer 2009;115:2765–74.
[51] Wedick NM, Mantzoros CS, Ding EL, Brennan AM, Rosner B, Rimm EB, et al. The effects of caffeinated and decaffeinated coffee on sex hormone-binding globulin and endogenous sex hormone levels: a randomized controlled trial. Nutr J 2012;11:86.
[52] Ferrini RL, Barrett-Connor E. Caffeine intake and endogenous sex steroid levels in postmenopausal women. The Rancho Bernardo Study. Am J Epidemiol 1996;144:642–4.
[53] Tworoger SS, Missmer SA, Barbieri RL, Willett WC, Colditz GA, Hankinson SE. Plasma sex hormone concentrations and subsequent risk of breast cancer among women using postmenopausal hormones. J Natl Cancer Inst 2005;97:595–602.
[54] Tamimi RM, Byrne C, Colditz GA, Hankinson SE. Endogenous hormone levels, mammographic density, and subsequent risk of breast cancer in postmenopausal women. J Natl Cancer Inst 2007;99:1178–87.
[55] Kaaks R, Berrino F, Key T, Rinaldi S, Dossus L, Biessy C, et al. Serum sex steroids in premenopausal women and breast cancer risk within the European Prospective Investigation into Cancer and Nutrition (EPIC). J Natl Cancer Inst 2005;97:755–65.
[56] Easton DF, Ford D, Bishop DT. Breast and ovarian cancer incidence in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. Am J Hum Genet 1995;56:265–71.
[57] Foulkes WD, Metcalfe K, Sun P, Hanna WM, Lynch HT, Ghadirian P, et al. Estrogen receptor status in BRCA1- and BRCA2-related breast cancer: the influence of age, grade, and histological type. Clin Cancer Res 2004;10:2029–34.
[58] Hill AB. The Environment and Disease: Association or Causation? Proc R Soc Med 1965;58:295–300.
[59] Lopez-Garcia E, Rodriguez-Artalejo F, Rexrode KM, Logroscino G, Hu FB, van Dam RM. Coffee consumption and risk of stroke in women. Circulation 2009;119:1116–23.

Please cite this article as: Jiang W, et al, Coffee and caffeine intake and breast cancer risk: An updated dose–response meta-analysis of 37 published studies, Gynecol Oncol (2013), http://dx.doi.org/10.1016/j.ygyno.2013.03.014

EXHIBIT “E”

SUPERIOR COURT OF THE STATE OF CALIFORNIA

FOR THE COUNTY OF LOS ANGELES

COUNCIL FOR EDUCATION AND RESEARCH ON TOXICS, a California corporation, acting as a private attorney general in the public interest; Plaintiff, vs. STARBUCKS CORPORATION, a Washington corporation; et al., Defendants.	CASE NO. BC435759 **STATEMENT OF DECISION ON TRIAL (PHASE ONE)** **(Defendants' No Significant Risk Level and Constitutional Affirmative Defenses)**
COUNCIL FOR EDUCATION AND RESEARCH ON TOXICS, a California corporation, acting as a private attorney general in the public interest, Plaintiff, vs. BRAD BARRY COMPANY, LTD., a California corporation, et al., Defendants.	

Trial on Phase I of this case concerning Defendants' affirmative defenses of "no significant risk level," First Amendment, and federal preemption proceeded on September 8, 2014. Testimony was presented, documentary evidence introduced, and

argument by counsel heard on September 8, 9, 10, 11, 12, 17, 18, 22, 29, 30; October 1, 6, 7, 8, 14, 20, 21, 22, 23, 27, 28; November 3 and 4, 2014. Final oral argument was presented on April 9, 2015, at which time the matter was taken under submission.

Having considered all the testimonial and documentary evidence, as well as the written briefs and argument of counsel, and being fully advised in the premises, the Court now renders its Proposed Statement of Decision.

I. PROCEDURAL BACKGROUND

1. On April 13, 2010, Plaintiff Council for Education and Research on Toxics (referred to herein as "Plaintiff" or "CERT"), a California corporation, acting as a private attorney general in the public interest, instituted Los Angeles Superior Court Case No. BC435759 against nineteen (19) defendants allegedly selling ready-to-drink coffee to millions of customers throughout the State of California.

2. On April 22, 2010, Plaintiff filed a First Amended Complaint alleging causes of action for (1) violations of Proposition 65 (Health & Safety Code, section 25249.6)[1/] and (2) declaratory relief.

3. On May 9, 2011, Plaintiff filed Los Angeles Superior Court Case No. BC461182 against forty-six (46) additional defendants, alleging causes of action for violation of Proposition 65 and declaratory relief.

4. With the addition of more defendants, a total of ninety-one (91) defendants appeared in both actions.

[1/] Unless otherwise indicated, all code sections refer to the Health & Safety Code.

5. In essence, Plaintiff claimed in the two actions that, in violation of Proposition 65 (the "Safe Drinking Water and Toxic Enforcement Act of 1986"), Defendants, sellers of ready-to-drink coffee, failed to provide warnings to consumers that the coffee sold contained high levels of acrylamide, a toxic and carcinogenic chemical.

6. Defendants filed answers to the complaints, denying the material allegations thereof and asserting various affirmative defenses, including: a) the statutory defense of "no significant risk level"; b) violation of the First Amendment to the Constitution (right of free speech); and c) federal preemption (Supremacy Clause).

7. On May 1, 2013, the Court ordered that Case Nos. BC 435759 and BC 461182 be consolidated for all purposes.

8. The Court has ordered that:

a) trial in the matter be bifurcated;
b) Phase I of the trial cover Defendants' affirmative defenses of (1) "no significant risk level"; (2) First Amendment; and (3) federal preemption;
c) Phase I of trial be litigated by Defendants Green Mountain Coffee Roasters, Inc., The J.M. Smucker Company, Kraft Foods Global, and Starbucks Corporation; and
d) all other Defendants be bound by the Court's final rulings regarding the issues decided in Phase I of the trial.

II. STATUTORY AND REGULATORY FRAMEWORK

9. Proposition 65 "was enacted by a citizen initiative" in 1986.

10. In enacting Proposition 65, the People of California found "that hazardous chemicals pose a serious potential threat to their health and well-being, that state government agencies have failed to provide them with adequate protection, and that these failures have been serious enough to lead to investigations by federal agencies of the administration of California's toxic protection programs."

11. By approving Proposition 65, the People of California also declared their rights "[t]o be informed about exposures to chemicals that cause cancer, birth defects, or other reproductive harm. . . . [and] [t]o secure strict enforcement of the laws controlling hazardous chemicals and deter actions that threaten public health and safety. . . ."

12. Proposition 65 (Health & Safety Code, section 25249.6) provides:

> "**Required warning before exposure to chemicals known to cause cancer or reproductive toxicity.**
>
> No person in the course of doing business shall knowingly and intentionally expose any individual to a chemical known to the state to cause cancer or reproductive toxicity without first giving clear and reasonable warning to such individual, except as provided in Section 25249.10."

13. Proposition 65 is "a remedial statute" that is to be construed broadly to accomplish its protective purposes. (*People ex rel. Lungren v. Superior Court* (1996) 14 Cal.4th 294, 314.)

14. Section 25249.8(a) states:

> "**List of chemicals known to cause cancer or reproductive toxicity.**

"On or before March 1, 1987, the Governor shall cause to be published a list of those chemicals **known to the state to cause cancer** or reproductive toxicity within the meaning of this chapter, and he shall cause such list to be revised and republished in light of additional knowledge at least once per year thereafter . " (Emphasis added)

15. Subsection (b) of section 25249.8 states:

"**A chemical is known to the state to cause cancer** . . . if in the opinion of the state's qualified experts it has been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer . . . or if a body considered to be authoritative by such experts has formally identified it as causing cancer. . . or if an agency of the state or federal government has formally required it to be labeled or identified as causing cancer. . . ." (Emphasis added)

16. Title 27, California Code of Regulations ("CCR"),[2/] section 25102 provides the following definitions:

"The 'Act' means the Safe Drinking Water and Toxic Enforcement Act of 1986 (Health and Safety Code Sections 25249.5 et seq.) which was originally adopted by California voters as Proposition 65 on November 4. 1986."

'Lead agency' means the Office of Environmental Health Hazard Assessment . . . ."

[2/] All references to CCR are references to Title 27 of the California Code of Regulations.

'Listed chemical' means a chemical listed pursuant to Section 25249.8(a) of the Act."

17. CCR 25305 provides for the powers and duties of the Carcinogen Identification Committee as follows:

"(a) As an advisory body to the Governor and the lead agency, the Carcinogen Identification Committee may undertake the following activities:

(1) Render an opinion . . . as to whether specific chemicals have been clearly shown, through scientifically valid testing according to generally accepted principles, to cause cancer.

(2) Identify bodies which are considered to be authoritative and which have formally identified chemicals as causing cancer.

(3) Identify specific chemicals that are required by state or federal law to have been tested for potential to cause cancer but which have not been adequately tested.

(4) Review or propose standards and procedures for determining carcinogenicity of chemicals.

(5) Review or propose standards, procedures and definitions related to the implementation, administration or interpretation of the Act . . . .

(6) Review the scientific basis for proposed **No Significant Risk Levels (NSRLs)** and other regulations proposed for Sections 25701 through 25721 (No Significant Risk Levels)." (Emphasis added)

18. CCR 25306 provides:

"Chemicals Formally Identified by Authoritative Bodies

(a) Pursuant to Section 25249.8(b) of the Act, a chemical is known to the state to cause cancer or reproductive toxicity if the lead agency determines that an authoritative body has formally identified the chemical as causing cancer or reproductive toxicity, as specified in this section.

(b) A "body considered to be authoritative" is an agency or formally organized program or group which utilizes one of the methods set forth in subsection (d), for the identification of chemicals, and which the Carcinogen Identification Committee has identified as having expertise in the identification of chemicals as causing cancer . . . . For purposes of this section, "authoritative body" means either a "body considered to be authoritative" in the identification of chemicals as causing cancer by the Carcinogen Identification Committee . . . .

(c) The lead agency shall determine which chemicals have been formally identified by an authoritative body as causing cancer . . .

(d) For purposes of this section a chemical is "formally identified" by an authoritative body when the lead agency determines that:

(1) the chemical has been included on a list of chemicals causing cancer or reproductive toxicity issued by the authoritative body; or is the subject of a report which is published by the authoritative body and which concludes that the chemical causes cancer or reproductive toxicity . . .

***

(e) For purposes of this section, "as causing cancer" means that either of the following criteria has been satisfied:

(1) Sufficient evidence of carcinogenicity exists from studies in humans . . . .

(2) Sufficient evidence of carcinogenicity exists from studies in experimental animals . . . .

(f) The lead agency shall find that a chemical does not satisfy the definition of "as causing cancer" if scientifically valid data which were not considered by the authoritative body clearly establish that the chemical does not satisfy the criteria of subsection (e), paragraph (1) or subsection (e), paragraph (2).

***

(m) The following have been identified as authoritative bodies for the identification of chemicals as causing cancer:

(1) International Agency for Research on Cancer

(2) National Institute for Occupational Safety and Health

(3) National Toxicology Program

(4) U.S. Environmental Protection Agency

(5) U.S. Food and Drug Administration" (Emphasis added)

19. Health & Safety Code, Section 25249.10 provides:

"Exemption from warning requirement

Section 25249.6 shall not apply to any of the following:

(a) An exposure for which federal law governs warning in a manner that preempts state authority.

***

(c) An exposure for which the person responsible can show that the exposure poses **no significant risk** assuming **lifetime exposure** at the **level in question** for substances known to the state to cause cancer, . . . **based on**

evidence and **standards** of **comparable scientific validity** to **the evidence and standards which form** the **scientific** basis **for the listing of such chemical** pursuant to subdivision (a) of Section 25249.8. In any action brought to enforce Section 25249.6, the **burden of showing that an exposure meets the criteria of this subdivision shall be on the defendant**." (Emphasis added)

20. As to the "**no significant risk level**" exemption, CCR 25701 provides:

"(a) The determination of whether a level of exposure to a chemical known to the state to cause cancer poses **no significant risk for purposes of Section 25249.10(c) of the Act shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of the chemical as known to the state to cause cancer**. Nothing in this article shall preclude a person from using evidence, standards, risk assessment methodologies, principles, assumptions or levels not described in this article to establish that a level of exposure to a listed chemical poses no significant risk." (Emphasis added)

21. CCR 25703, regarding **Quantitative Risk Assessment**, states:

"(a) A quantitative risk assessment which conforms to this section shall be deemed to determine the **level of exposure** to a listed chemical which, assuming daily exposure at that level, poses no significant risk. The **assessment shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for listing the chemical as known to the state to cause cancer** . . . (Emphasis added)

***

"(b) For chemicals assessed in accordance with this section, the risk level which represents no significant risk shall be one which is calculated to result in one excess case of cancer in an exposed population of 100,000, assuming **lifetime exposure** at the **level in question**, except where sound considerations of public health support an alternative level . . . ." (Emphasis added)

22. In reference to the **level of exposure to chemicals causing cancer**, CCR 25721(a) provides:

"For the purposes of the Act, "**level in question**" means the chemical concentration of a listed chemical for the exposure in question. The exposure in question includes the exposure for which the person in the course of doing business is responsible and does not include exposure to a listed chemical from any other source or product." (Emphasis added)

23. As to "**lifetime exposure**" CCR 25721(b) provides:

"For purposes of the Act, "**lifetime exposure**" means the reasonably anticipated rate of exposure for an individual to a given medium of exposure measured over a lifetime of seventy years." (Emphasis added)

24. The methodology for determining **level of exposure** is set forth in CCR 25721(c):

"For purposes of Section 25249.10(c) of the Act, the **level of exposure** to a chemical listed as causing cancer, assuming **lifetime exposure** at the **level in question**, shall be determined by multiplying the **level in question** (stated in terms

of a concentration of a chemical in a given medium) times the reasonably anticipated rate of exposure for an individual to the given medium of exposure measured over a lifetime of seventy years." (Emphasis added)

25. With respect to exposures to consumer products, such as coffee, CCR 25721(d)4 states:

"For exposures to consumer products, lifetime exposure shall be calculated using the average rate of intake or exposure for average users of the consumer product, and not on a per capita basis for the general population . . ."

III. ACRYLAMIDE

26. The Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency has listed acrylamide as a chemical known to the state to cause cancer since 1990, pursuant to the authoritative body method set forth in the California Code of Regulations.

27. Acrylamide was listed as a chemical known to the State of California to cause cancer based on formal identification of acrylamide as a carcinogen by the International Agency for Research on Cancer and the U.S. Environmental Protection Agency.

28. The parties do not dispute that acrylamide is listed by the State of California as a chemical causing cancer.

IV. ACRYLAMIDE IN COFFEE

29. When coffee beans are roasted, a chemical reaction occurs (the Maillard reaction)

causing the asparagine and sugars in green coffee beans to produce the chemical acrylamide. As coffee is brewed, the acrylamide in the ground roasted coffee beans dissolves in water, resulting in acrylamide being present in brewed coffee.

30. The parties do not dispute that roasting coffee causes the release of the chemical acrylamide and that brewed coffee contains acrylamide.

V. THE "NO SIGNIFICANT RISK LEVEL" DEFENSE

31. The "no significant risk level" defense in a Proposition 65 case is a statutory defense that provides an exemption to the cancer hazard warning requirement of Health & Safety Code § 25249.6 for "[a]n exposure for which the person responsible can show that the exposure poses no significant risk assuming lifetime exposure at the level in question for substances known to the state to cause cancer . . . , based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of such chemical pursuant to subdivision (a) of Section 25249.8." (Section 25249.10)

32. The "no significant risk level" defense must be analyzed in terms of "an exposure for which . . . there is no significant risk . . . **for substances known to the state to cause cancer** . . ." (Emphasis added) (Health & Safety Code, § 25249.10) In this case, the substance in question is acrylamide.

33. "Risk assessment" is a systematic scientific approach used to characterize the nature of an adverse effect, and the probability that such adverse effect would occur in exposed individuals or populations.

34. Risk assessments are undertaken to provide the information necessary for

governmental agencies to make risk management decisions regarding the extent to which human exposure should be limited or controlled for an agent which has an identifiable adverse effect on segments of the population.

35. Risk assessments are undertaken to assess both cancer and non-cancer risks to humans.

36. There are two types of cancer risk assessments: qualitative and quantitative.

37. Qualitative cancer risk assessments are performed to determine whether a chemical or other substance (an "agent") is a carcinogen, i.e., can cause cancer.

38. Quantitative cancer risk assessments are undertaken to determine the level of risk of cancer from exposure to a carcinogen.

39. A quantitative cancer risk assessment is necessary to quantify the level or degree of risk of cancer from exposure to a carcinogen.

40. When attempting to determine the risk of cancer from a chemical mixture, scientific expert risk assessors identify the carcinogen(s) in the mixture and quantify the risk of human cancer presented by the carcinogen(s) in the mixture, unless the mixture itself has been deemed to be carcinogenic.

41. Since the level of exposure to a chemical listed as causing cancer (e.g., acrylamide) must be determined by multiplying the level in question (stated in terms of a concentration of a chemical in a given medium) times the reasonably anticipated rate of exposure for an individual to the given medium of exposure measured over a lifetime of seventy years (CCR 25721(c)), the focus on the level of risk in this case must be based on the

concentration of acrylamide in coffee.

42. Defendants did not present sufficient credible evidence of the degree of risk posed by acrylamide in coffee pursuant to a quantitative risk assessment (the only type of risk assessment utilized by the relevant credible scientific community to assess the risk of a carcinogen in a mixture), to determine by a preponderance of evidence the level of risk of cancer from exposure to acrylamide in coffee.

43. Defendants' evidence of risk assessment was based largely on epidemiology studies that were inadequate to evaluate risks of cancer from exposure to acrylamide in coffee.

44. To establish the "no significant risk level" defense, Defendants must prove the absence of significant risk of cancer at the "level in question" for the chemical "known to the state to cause cancer."

45. Defendants' risk assessment was not based on the "level in question," meaning the chemical concentration of acrylamide in the medium of coffee. Defendants' risk assessment therefore failed to satisfy the statutory requirement.

46. The "no significant risk level" defense must also be "based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of such chemical pursuant to subdivision (a) of Section 25249.8." (Section 25249.10)

47. Defendants presented evidence of an assessment of the mixture of coffee, rather than an assessment of the chemical acrylamide, as such, in the medium of coffee. However, coffee was not a "substance[s] known to the state to cause cancer."

Defendants' risk assessment was therefore insufficient to satisfy the statutory requirement that the risk assessment be for the chemical "known to the state to cause cancer."

48. The foundation of Defendants' risk assessment was an evaluation of coffee as a mixture. However, the basis for the State of California listing acrylamide as a chemical known to the state to cause cancer was an evaluation of the chemical acrylamide and its carcinogenicity. As a consequence, the evaluation performed by Defendants was not comparable to the required analyses undertaken for the listing of acrylamide as a carcinogen by the state.

49. Defendants' argument that other constituents or ingredients in coffee eliminate or reduce the cancer risk of acrylamide in coffee lacked evidentiary scientific support, and was based largely on speculation and conjecture.

50. In sum, Defendants have failed to prove their "no significant risk level" defense. Accordingly, this defense is adjudicated against Defendants.

VI. FIRST AMENDMENT DEFENSE

51. Defendants argue that a required warning by Proposition 65 for acrylamide in coffee would violate their freedom of speech rights under the First Amendment to the United States Constitution.

52. The speech subject to Defendants' First Amended defense is commercial speech since it arises from Defendants' commercial activities in selling coffee.

53. Commercial speech is entitled to only "limited" and "subordinate" First Amendment protection.

54. Where a business is required to disclose information about its products or services to the public under state law, a more lenient test as to the constitutionality of mandated product information is appropriate under the First Amendment, because a company's interest in not providing factual information about its products is "minimal." A proponent for enforcement of a state law affecting the right of free speech in a commercial context need only establish that the commercial product disclosure or warning requirement is "reasonably related" to an underlying state interest. (*Zauderer v. Office of Disciplinary Counsel* (1985) 471 U.S. 620, 651.)

55. A Proposition 65 warning requirement for the presence of acrylamide passes this "reasonably related" test for several reasons:

a) The warning fulfills a legitimate state interest of informing the public of "exposure to chemicals that cause cancer, birth defects, or other reproductive harm."

b) The warning requirement is reasonably related to the state's interest in providing critical health and safety information to the public. The law requires businesses to provide the warnings directly, which is reasonable because a business is more likely to know, or be able to ascertain, the contents of its own products.

c) The warning that a chemical known to the state may cause cancer is not false or misleading.

56. Defendants' First Amendment defense is also dependent on the success of their "no significant risk level" defense. Since the Court finds that Defendants failed to prove their "no significant risk level" defense by a preponderance of the evidence, the Court finds that Defendants' First Amendment defense likewise fails.

57. Defendants have failed to establish their First Amendment affirmative defense. Accordingly, the defense is adjudicated against Defendants.

VII. PREEMPTION DEFENSE

58. The United States Supreme Court has held that under the Supremacy Clause (U.S. Const. Art. VI, cl.2), the federal government may preempt state law under three circumstances: (1) express preemption, where Congress explicitly defines the extent to which federal law preempts state law; (2) field preemption, where Congress intends federal law to exclusively occupy an area of law, and the federal law is so pervasive as to leave no room for the states to supplement the area; and (3) conflict preemption, where there is an actual conflict between federal and state law. (*English v. General Electric* (1990) 496 U.S. 72, 78-79.)

59. No federal statute or regulation expressly preempts Proposition 65.

60. Defendants have not asserted, and no evidence has been presented, that field preemption exists in this case.

61. There is no conflict between a Proposition 65 warning for acrylamide in coffee and the Federal Food, Drug and Cosmetic Act, or any other federal statute or regulation. The Federal Drug Administration has not mandated any warnings for acrylamide in food, and there is no other federal statute, or regulation requiring warnings for acrylamide in coffee. Defendants have not presented any evidence of a conflicting federal regulation or statute.

62. Defendants' argument that a Proposition 65 warning would violate the Federal Food, Drug and Cosmetic Act's misbranding provisions lacks merit. Acrylamide was placed on the Governor of California's list of chemicals known to cause cancer on January 1, 1990. (CCR 27001) Defendants do not dispute that acrylamide is present in their coffee. A Proposition 65 warning for acrylamide in coffee is therefore truthful and

can be provided in a manner that is neither false nor misleading, consistent with federal law.

63. Defendants' preemption defense is also dependent upon the success of their "no significant risk level" defense. Because Defendants failed to prove their "no significant risk level" defense by a preponderance of the evidence, the Court finds that their preemption defense likewise fails.

64. Defendants have failed to establish their federal preemption defense, which is therefore adjudicated against Defendants.

VIII. CONCLUSION

65. Defendants have the burden of proof to establish their defenses by preponderance of the evidence.

66. Defendants have failed to meet their burden of proof on their affirmative defenses of "no significant risk level"; First Amendment; and federal preemption.

67. Accordingly, the Court rules in favor of Plaintiff and against Defendants on the affirmative defenses of "no significant risk level"; First Amendment; and federal preemption.

DATED: September 11, 2015

HONORABLE ELIHU M. BERLE
JUDGE OF THE SUPERIOR COURT

EXHIBIT “F”

SUPERIOR COURT OF THE STATE OF CALIFORNIA

FOR THE COUNTY OF LOS ANGELES

COUNCIL FOR EDUCATION AND RESEARCH ON TOXICS, a California corporation, acting as a private attorney general in the public interest; Plaintiff, vs. STARBUCKS CORPORATION, a Washington corporation; et al., Defendants. COUNCIL FOR EDUCATION AND RESEARCH ON TOXICS, a California corporation, acting as a private attorney general in the public interest, Plaintiff, vs. BRAD BARRY COMPANY, LTD., a California corporation, et al., Defendants.	CASE NO. BC435759 **STATEMENT OF DECISION AFTER TRIAL (PHASE II)** **(Defendants' Alternative Significant Risk Level Affirmative Defense)**

Trial on Phase II of this case concerning Defendants' affirmative defense of "Alternative Significant Risk Level," proceeded on September 5, 2017. Testimony was presented, documentary evidence introduced, and argument by counsel heard on

September 5, 6, 7, 8, 11, 12, 18, 19, 20, 25, 26; October 2, 3; and November 21, 2017. The parties thereafter submitted post trial briefings on December 22, 2017 and January 19, 2018.

Having considered all the testimonial and documentary evidence, as well as the written briefs and argument of counsel, and being fully advised in the premises, the Court now renders its Statement of Decision (Phase II).

I. PROCEDURAL BACKGROUND

1. On April 13, 2010, Plaintiff Council for Education and Research on Toxics (referred to herein as "Plaintiff" or "CERT"), a California corporation, acting as a private attorney general in the public interest, instituted Los Angeles Superior Court Case No. BC435759 against nineteen (19) defendants allegedly selling ready-to-drink coffee to millions of customers throughout the State of California.

2. On April 22, 2010, Plaintiff filed its First Amended Complaint alleging causes of action for (1) violations of Proposition 65 (Health & Safety Code, section 25249.6)[1] and (2) declaratory relief.

3. On May 9, 2011, Plaintiff filed Los Angeles Superior Court Case No. BC461182 against forty-six (46) additional defendants, alleging causes of action for violation of Proposition 65 and declaratory relief.

4. With the addition of more defendants, a total of ninety-one (91) defendants appeared in both actions.

[1] Unless otherwise indicated, all code sections refer to the Health & Safety Code.

5. In essence, Plaintiff claims that Defendants failed to provide warnings to consumers that the coffee which they sold contained high levels of acrylamide, a toxic and carcinogenic chemical, in violation of Proposition 65 (the "Safe Drinking Water and Toxic Enforcement Act of 1986").

6. Defendants filed answers to the complaints, denying the material allegations thereof and asserting various affirmative defenses, including: a) the statutory defenses of "no significant risk level" and "alternative risk level"; b) violation of the First Amendment to the United States Constitution (right of free speech); and c) federal preemption (Supremacy Clause).

7. On May 1, 2013, the Court ordered that Cases Nos. BC 435759 and BC 461182 be consolidated for all purposes, and ordered that:

a) trial in the matter be bifurcated;
b) Phase I of the trial cover Defendants' affirmative defenses of (1) "no significant risk level"; (2) First Amendment; and (3) federal preemption;
c) Phase II address the issue of Defendants' affirmative defense of "alternative significant risk level."

8. Pursuant to stipulation, many of the Defendants agreed that Phase I of trial would be litigated by Defendants Green Mountain Coffee Roasters, Inc., the J.M. Smucker Company, Kraft Foods Global, and Starbucks Corporation; and that the stipulating Defendants would be bound by the Court's final rulings regarding the issues decided in Phase I of the trial. Defendant Dunkin' Brands, Inc. was not a party in either action at the time of the Phase I trial and thus did not agree to be bound by the decision in that phase.

II. STATUTORY AND REGULATORY FRAMEWORK

9. Proposition 65 was enacted by a citizen initiative in 1986.

10. In *People ex rel. Lungren v. Superior Court* (1996) 14 Cal.4th 294, the California Supreme Court described the purposes of Proposition 65 at 306:

> "The purposes of Proposition 65 are stated in the preamble to the statute, section 1, which declares in pertinent part: 'The people of California find that hazardous chemicals pose a serious potential threat to their health and well-being, that state government agencies have failed to provide them with adequate protection, and that these failures have been serious enough to lead to investigations by federal agencies of the administration of California's toxic protection programs. The people therefore declare their rights: (a) to protect themselves and the water they drink against chemicals that cause cancer, birth defects, or other reproductive harm.' [Citation.]"

11. By approving Proposition 65, the People of California also declared their rights "[t]o be informed about exposures to chemicals that cause cancer, birth defects, or other reproductive harm. . . ." and "[t]o secure strict enforcement of the laws controlling hazardous chemicals and deter actions that threaten public health and safety. . . ." (Historical and Statutory Notes, West's Annotated California Codes, § 25249.5.)

12. Proposition 65 (section 25249.6) provides:

> *"Required warning before exposure to chemicals known to cause cancer or reproductive toxicity.*

No person in the course of doing business shall knowingly and intentionally expose any individual to a chemical known to the state to cause cancer or reproductive toxicity without first giving clear and reasonable warning to such individual, except as provided in Section 25249.10."

13. Section 25249.8(a) states:

"*List of chemicals known to cause cancer or reproductive toxicity.* On or before March 1, 1987, the Governor shall cause to be published a list of those chemicals *known to the state to cause cancer* or reproductive toxicity within the meaning of this chapter, and he [sic] shall cause such list to be revised and republished in light of additional knowledge at least once per year thereafter." (Emphasis added.)

14. Subsection (b) of section 25249.8 states:

"*A chemical is known to the state to cause cancer* . . . if in the opinion of the state's qualified experts it has been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer . . . or if a body considered to be authoritative by such experts has formally identified it as causing cancer. . . or if an agency of the state or federal government has formally required it to be labeled or identified as causing cancer. . . ." (Emphasis added.)

15. Title 27 California Code of Regulations ("CCR"),[2] section 25102, provides the following definitions:

[2] All references to CCR are references to Title 27 of the California Code of Regulations.

"The 'Act' means the Safe Drinking Water and Toxic Enforcement Act of 1986 (Health and Safety Code Sections 25249.5 et seq.) which was originally adopted by California voters as Proposition 65 on November 4. 1986.

"Committee' means the carcinogen Identification Committee and the Developmental and Reproductive Toxicant (DART) Identification Committee of the Office of Environmental Health Hazard Assessment Science Advisory Board.

"Lead agency' means the Office of Environmental Health Hazard Assessment . . . .

"Listed chemical' means a chemical listed pursuant to Section 25249.8(a) of the Act."

16. CCR section 25305 provides for the powers and duties of the Carcinogen Identification Committee as follows:

"(a) As an advisory body to the Governor and the lead agency, the Carcinogen Identification Committee may undertake the following activities:

(1) Render an opinion . . . as to whether specific chemicals have been clearly shown, through scientifically valid testing according to generally accepted principles, to cause cancer.

(2) Identify bodies which are considered to be authoritative and which have formally identified chemicals as causing cancer.

(3) Identify specific chemicals that are required by state or federal law to have been tested for potential to cause cancer but which have not been adequately tested.

(4) Review or propose standards and procedures for determining carcinogenicity of chemicals.

(5) Review or propose standards, procedures and definitions related to the implementation, administration or interpretation of the Act . . . .

(6) Review the scientific basis for proposed *No Significant Risk Levels (NSRLs)* and other regulations proposed for Sections 25701 through 25721 (No Significant Risk Levels)." (Emphasis added.)

17. CCR section 25306 provides:

"Chemicals Formally Identified by Authoritative Bodies

(a) Pursuant to Section 25249.8(b) of the Act, a chemical is known to the state to cause cancer or reproductive toxicity if the lead agency determines that an authoritative body has formally identified the chemical as causing cancer or reproductive toxicity, as specified in this section."

18. Section 25249.10 provides:

"*Exemption from warning requirement*

Section 25249.6 shall not apply to any of the following:

(a) An exposure for which federal law governs warning in a manner that preempts state authority.

***

(c) An exposure for which the person responsible can show that the exposure poses *no significant risk* assuming *lifetime exposure* at the *level in question* for substances known to the state to cause cancer, . . . *based on evidence* and *standards of comparable scientific validity* to *the evidence and standards which form* the *scientific* basis *for the listing of such chemical* pursuant to subdivision (a) of Section 25249.8. In any action

brought to enforce Section 25249.6, the *burden of showing that an exposure meets the criteria of this subdivision shall be on the defendant.*" (Emphasis added.)

19. As to the "*no significant risk level*" exemption, CCR section 25701 provides:

"(a) The determination of whether a level of exposure to a chemical known to the state to cause cancer poses *no significant risk for purposes of Section 25249.10(c) of the Act shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of the chemical as known to the state to cause cancer*. Nothing in this article shall preclude a person from using evidence, standards, risk assessment methodologies, principles, assumptions or levels not described in this article to establish that a level of exposure to a listed chemical poses no significant risk." (Emphasis added.)

20. For a determination of the level exposure to a listed chemical, CCR section 25703 states with regard to *Quantitative Risk Assessment*:

"(a) A quantitative risk assessment which conforms to this section shall be deemed to determine the *level of exposure* to a listed chemical which, assuming daily exposure at that level, poses no significant risk. The *assessment shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for listing the chemical as known to the state to cause cancer . . .* (Emphasis added.)

***

"(b) For chemicals assessed in accordance with this section, the risk level which represents no significant risk shall be one which is calculated to result in one excess case of cancer in an exposed population of 100,000, assuming *lifetime exposure* at the *level in question*, except where sound considerations of public health support an *alternative level* . . . ." (Emphasis added.)

21. As to "*lifetime exposure*" CCR section 25721(b) provides:

"For purposes of the Act, '*lifetime exposure*' means the reasonably anticipated rate of exposure for an individual to a given medium of exposure measured over a lifetime of seventy years." (Emphasis added.)

22. In reference to the *level of exposure to chemicals causing cancer*, CCR section 25721(a) provides:

"For the purposes of the Act, '*level in question*' means the chemical concentration of a listed chemical for the exposure in question. The exposure in question includes the exposure for which the person in the course of doing business is responsible and does not include exposure to a listed chemical from any other source or product." (Emphasis added.)

23. The methodology for determining *level of exposure* is set forth in CCR section 25721(c):

"For purposes of Section 25249.10(c) of the Act, the *level of exposure* to a chemical listed as causing cancer, assuming *lifetime exposure* at the *level in question*, shall be determined by multiplying the *level in question* (stated in terms of a concentration of a chemical in a given medium) times the reasonably

anticipated rate of exposure for an individual to the given medium of exposure measured over a lifetime of seventy years." (Emphasis added.)

24. With respect to exposures to consumer products, such as coffee, CCR section 25721(d)(4) states:

"For exposures to consumer products, lifetime exposure shall be calculated using the average rate of intake or exposure for average users of the consumer product, and not on a per capita basis for the general population."

25. Proposition 65 is a remedial statute intended to protect the public and, therefore, is to be construed broadly to accomplish its protective purposes. (*Lungren, supra,* 14 Cal.4th at p. 314.)

26. "Generally, the rules that govern interpretation of statutes also govern interpretation of administrative regulations." (*Berkeley Hillside Preservation v. City of Berkeley* (2015) 60 Cal.4th 1086, 1097; accord *Hoitt v. Department of Rehabilitation* (2012) 207 Cal.App.4th 513, 523; *Price v. Starbucks Corporation* (2011) 192 Cal.App.4th 1136, 1145.)

27. An administrative regulation that provides an exemption to Proposition 65 must be narrowly construed so as not to "frustrate the purpose of the statute which it implements." (*Mateel Environmental Justice Foundation v. Edmund A. Gray Co.* (2004) 115 Cal.App.4th 8, 24, citing *Lungren, supra*, 14 Cal.4th at p. 324 [as a "remedial statute," Proposition 65 must be "construed broadly to accomplish [its] protective purpose"].)

28. In *Exxon Mobile Corp. v. Office of Environmental Health Hazard Assessment* (2009) 169 Cal.App.4th 1264, a case in which plaintiff challenged the listing under

Proposition 65 of a chemical known to cause reproductive toxicity, the Court of Appeal discussed the deference that courts should give to an agency's interpretation of their regulations at 1280:

> "As a starting point, the interpretation of an administrative regulation is subject to the same principles as the interpretation of a statute . . . . [W]here the language of the regulation is ambiguous, it is appropriate to consider the agency's interpretation. [Citation.] Indeed, we defer to an agency's interpretation of a regulation involving its area of expertise, unless the interpretation flies in the face of the clear language and purpose of the interpretive provision." (Citations and quotation marks omitted.)

III. ACRYLAMIDE

29. Acrylamide has been listed under Proposition 65 as a chemical known to the State of California to cause cancer since 1990.

30. Acrylamide was listed based on its formal identification as a carcinogen by the International Agency for Research on Cancer and the U.S. Environmental Protection Agency.

31. The parties do not dispute that acrylamide is listed by the State of California as a chemical causing cancer.

IV. ACRYLAMIDE IN COFFEE

32. When coffee beans are roasted, a chemical reaction occurs (the Maillard reaction) causing the asparagine and sugars in green coffee beans to produce the chemical

acrylamide. As coffee is brewed, the acrylamide in the ground roasted coffee beans dissolves in water, resulting in acrylamide being present in brewed coffee.

33. The parties do not dispute that roasting coffee causes the release of the chemical acrylamide, and that brewed coffee contains acrylamide.

34. Defendants do not dispute that during at least some of the statutory period they failed to provide warnings to consumers that coffee which they sold contained acrylamide.

V. CONCLUSIONS FROM PHASE I OF THE TRIAL

35. In Phase I of the trial in this case, the Court concluded that Defendants failed to meet their burden of proof by preponderance of evidence on their affirmative defenses of "no significant risk level," First Amendment, and federal preemption to avoid the requirement of cancer warning labels as to the existence of acrylamide in brewed coffee.

VI. PROCEEDINGS ON PHASE II OF TRIAL

36. On February 26, 2016, Plaintiff and most of the Defendants stipulated that defenses other than the "alternative significant risk level" defense would be dismissed as to liability issues, but would be preserved for remedy issues only.

37. Thereafter, most of the Defendants agreed to Stipulations of Fact that served as the basis for Plaintiff's motion for summary adjudication of its prima facie case.

38. On June 1, 2016, the Court issued its Order Granting Motion for Summary Adjudication of Plaintiff's Prima Facie Case Against Stipulating Roaster Defendants; and

on April 20, 2016 the Court issued its Order Granting Motion for Summary Adjudication of Plaintiff's Prima Face Case Against Stipulating Retailer Defendants.

39. On September 5, 2017 trial commenced on Defendants' Alternative Significant Risk Level (ASRL) defense.

VII. THE ALTERNATIVE SIGNIFICANT RISK LEVEL (ASRL) DEFENSE

40. The ASRL affirmative defense is grounded on an exemption to the cancer warning requirement of Health and Safety Code section 25249.6 provided in Section 25249.10(c), which states that section 25249.6 shall not apply to "[a]n exposure for which the person responsible can show that the exposure poses on significant risk assuming lifetime exposure at the level in question for substances known to the state to cause cancer . . . ."

41. Pursuant to CCR, section 25701, subdivisions (a) and (b), "[t]he determination of whether a level of exposure to a chemical known to the state to cause cancer poses no significant risk for purposes of section 25249.10(c) . . . shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of the chemical as known to the state to cause cancer[,]" and "[a] level of exposure to a listed chemical, assuming daily exposure at that level, shall be deemed to pose no significant risk provided that the level is determined . . . [b]y means of a quantitative risk assessment that meets the standards described in CCR section 25703."

42. Defendants' "Alternative Significant Risk Level" (ASRL) defense is based upon their interpretation of CCR section 25703, subdivision (b)(1) "Quantitative Risk Assessment," a part of Proposition 65's implementing regulations.

43. CCR section 25703. Quantitative Risk Assessment.

(a) A quantitative risk assessment which conforms to this *section* shall be deemed to determine the level of exposure to a listed chemical which, assuming daily exposure at that level, poses no significant risk. The assessment shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for listing the chemical as known to the state to cause cancer . . .

* * *

(b) For chemicals assessed in accordance with this *section*, the risk level which represents no significant risk shall be one which is calculated to result in one excess case of cancer in an exposed population of 100,000, assuming lifetime exposure at the level in question, except where sound considerations of public health support an *alternative level*, as, for example:

(1) where chemicals in food are produced by cooking necessary to render the food palatable or to avoid microbiological contamination; . . ." (Emphasis added.)

44. "[I]t is well established that . . . section headings may properly be considered in determining legislative intent, and are entitled to considerable weight." (*People v. Hull* (1991) 1 Cal.4th 266, 272; accord *In re Carr* (1998) 65 Cal.App.4th 1525, 1530.)

45. In determining the intent of CCR section 25703, the Court may consider that this section is headed "Quantitative Risk Assessment," and the Court may accord "considerable weight" to this heading.

46. Subsection (a) of CCR section 25703 states: "A quantitative risk assessment which conforms to *this section* shall be deemed to determine the level of exposure to a listed chemical which, assuming daily exposure at that level, poses no significant risk. . . ."

(Emphasis added.)

47. Subsection (b) of CCR section 25703 does not state that a quantitative risk assessment is not required for carcinogens in cooked foods. Thus, subsection (b) cannot be construed as an exception to the quantitative risk assessment requirement.

48. Subsection (b) indicates that chemicals are to be "assessed in accordance with this *section*" (i.e., the entirety of the *section*, including the provisions of subsection (a) which specify how quantitative risk assessments must be done) and that "for chemicals assessed in accordance with this section, the risk level which represents *no significant risk*" can be "*an alternative level*" "where chemicals in food are produced by cooking necessary to render the food palatable or to avoid microbiological contamination," and where "sound considerations of public health *support* such an alternative level."

49. The Court concludes that to prove their ASRL defense, Defendants must proffer a quantitative risk assessment that satisfies the requirements of CCR section 25703 – the "Quantitative Risk Assessment" regulation.

50. Section 25703 allows a defendant to establish an exemption to liability by proving that exposure to the carcinogen in its product does not exceed an "alternative risk level" derived by a "quantitative risk assessment" where "sound considerations of public health support an alternative level."

51. In order to prevail on their alternative risk level defense in this case Defendants would have to: a) establish that acrylamide is created by cooking or processing necessary to render the coffee safe or palatable; b) demonstrate that "sound considerations of public health" justify applying an alternative (less strict) risk level; and c) present persuasive evidence of what would be an appropriate alternative risk level, taking into account the

identified public health considerations. If any of these three factors are absent, the alternative risk level defense would not apply.

52. Thus, in order for Defendants to succeed on their ASRL defense under CCR section 25703, Defendants must prove that (1) "sound considerations of public health support an alternative level" for exposure to acrylamide in their coffee products, (2) such "alternative level" is derived from a "quantitative risk assessment," and (3) that "assuming lifetime exposure" to the products, the exposure to acrylamide from Defendants' coffee products is below such "alternative level."

53. Proposition 65 provides an express exemption from liability for chemicals that occur naturally in food. However, such exemption does not apply to carcinogens that are formed during the cooking process of natural food.

54. The fact that Defendants do not intentionally add acrylamide to their products is not a defense to liability under Proposition 65.

55. The Act does not allow any categorical exemption from liability for failure to warn except based upon a specific numerical value (i.e., a level of a listed chemical) that is calculated by means of a quantitative cancer risk assessment conducted in accordance with the Act.

56. To quantify the risk of cancer from exposure to acrylamide in drinking coffee it is necessary to conduct a quantitative assessment of the risk of developing cancer from exposure to acrylamide in coffee.

57. The Health and Welfare Agency (the "Agency"), charged with implementing the Act at the time, in its Final Statement of Reasons, 22 California Code of Regulations,

Division 2, for CCR section 12703, stated that its ". . . intention is that, whatever method of cooking is chosen, the amount of cooking which is necessary to avoid bacterial contamination or to render the food palatable should provide a basis for the application of a risk level other than a risk of 1×10^{-5}. [1 in 100,000]" (Final Statement of Reasons, CCR § 12703, at p. 7.)

58. The Final Statement of Reasons also provided the following:

> "Prior to this regulatory action, interested parties . . . requested that the Agency prevent the potential of liability under the Act as a result of the cooking of food. A petition from thirteen food, drug, cosmetic and medical device organizations requested that the Agency provide that exposure to chemicals which result from cooking pose no significant risk. [Citation.] *This proposal was not adopted, however, because the Agency could not be certain that all exposures which result from all manner of cooking in fact pose no significant risk.*" (Final Statement of Reasons, CCR § 12703, at p. 5.)

59. The Agency's Report continued:

> a) "Several commenters to section 12501 of the regulations recommended that chemicals formed by cooking be considered as 'naturally occurring' chemicals which do not cause an exposure under the Act. [Citation.] This recommendation was also not adopted, since the definition of 'naturally occurring,' which was derived from federal regulation [ ], requires an absence of human activity, and cooking is a human activity." (Final Statement of Reasons, CCR § 12703, at p. 5.)

b) "This approach (assessment of the cancer risk and the health benefit to be obtained from the food) has the advantage of flexibility. It does not establish a rigid line with which businesses must comply or face liability. Necessary cooking may result in varying amounts of chemical by-products. To the extent that the cooking is necessary to avoid contamination or to render the food palatable, the level which is considered to pose no significant risk should vary with the level of chemical by-product, and the public health benefit to be obtained." (Final Statement of Reasons, CCR § 12703, at p. 6.)

c) "The Agency's intention is that, whatever method of cooking is chosen, the amount of cooking which is necessary to avoid bacterial contamination or to render the food palatable should provide a basis for the application of a risk level other than a risk of 1×10^{-5}." (Final Statement of Reasons, CCR § 12703, at p. 7.)

VIII. DEFENDANTS' EVIDENCE AT TRIAL

60. Defendants' risk assessment expert, Lorenz Rhomberg, Ph.D, did not calculate an ASRL for *acrylamide in coffee* by means of any quantitative cancer risk assessment.

61. Dr. Rhomberg's risk assessment was not based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for listing acrylamide pursuant to section 25249.8.

62. Although Dr. Rhomberg performed a quantitative risk assessment of acrylamide, he did not undertake a quantitative risk assessment for *acrylamide in coffee*. Hence, he did not perform a risk assessment for a carcinogen (acrylamide) in a mixture (coffee). Dr. Rhomberg failed to undertake the type of quantitative risk assessment that is

necessary to quantify the risk of cancer from exposure to acrylamide in coffee.

63. Dr. Rhomberg did not calculate an ASRL based on sound considerations of public health for exposure to acrylamide from consumption of coffee, as is required by CCR section 25703(b).

64. Rather than calculating an ASRL based on sound considerations of public health, Dr. Rhomberg simply did a quantitative risk assessment for acrylamide and applied it to calculate the 10^{-4} (1 in 10,000) risk level for humans.

65. Dr. Rhomberg's analysis is thus not "based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for listing." (Section 25249.10(c).)

66. Defendants relied on the testimony of Dr. David Kessler to provide a rationale for an ASRL that is 10 times greater than the No Significant Risk Level (NSRL) for acrylamide. Dr. Kessler provided two rationales for an ASRL that is 10 times greater than the NSRL for acrylamide (i.e., an ASRL based on a cancer risk of 10^{-4} rather than 10^{-5}): (1) that the FDA had regulated carcinogens in two foods (PCBs in fish and arsenic in rice) at the 10^{-4} standard rather than FDA's usual 10^{-6} standard; and (2) that the Office of Environmental Health Hazard Assessment (OEHHA) had once proposed (but ultimately rejected) regulating acrylamide in bread and cereal at a 10^{-4} level. These rationales lack scientific support, are not based on sound considerations of public health, and provide inadequate grounds for an alternative risk level.

67. Defendants did not present quantitative risk assessments for Defendants' individual products.

68. Defendants presented evidence of data generated by Covance Laboratories of the acrylamide concentrations in Defendants' brewed coffee products. This evidence was scientifically unreliable and inadmissible because the analytical chemistry method that Covance used to test Defendants' products was a novel and untested scientific technique that has not been generally accepted in the scientific community. (*People v. Kelly* (1976) 17 Cal.3d 24, 30-31; see *Sargon Enterprises, Inc., v. University of South Cal.* (2012) 55 Cal.4th 747, 769; *People v. Leahy* (1994) 8 Cal.4th 587, 604-13.)

69. Covance's analytical method was not executed using proper scientific procedures, and generated inaccurate results in its analyses. As a consequence, Covance's analytic data of the acrylamide levels of Defendants' brewed coffee products is also unreliable and inadmissible.

70. Defendants' witness who testified about the Covance data, Darryl Sullivan, is not academically qualified to explain the science underlying the method used by Covance or to testify whether the method is generally accepted in the scientific community. Thus, a proper foundation was not laid for the admissibility of the Covance data.

71. The testimony of Defendants' expert witness, Dr. Carolyn Scrafford, with respect to exposure assessment for each of Defendants' products, was based upon the scientifically unreliable and inadmissible Covance data of the acrylamide concentrations of Defendants' products.

72. Because the testimony of Defendants' expert, Dr. Scrafford, regarding exposure assessment, was based on unreliable data generated by Covance Laboratories of acrylamide levels in Defendants' brewed coffee products, her testimony is also without proper foundation and inadmissible.

IX. DEFENDANTS' BURDEN OF PROVING THEIR ALTERNATIVE RISK LEVEL DEFENSE

73. "[T]he burden of showing that an exposure meets *the criteria*" of the Alternative Significant Risk Level exemption "shall be on the defendant." (Section 25249.10, emphasis added.)

74. Defendants did not offer substantial evidence to quantify any minimum amount of acrylamide in coffee that might be necessary to reduce microbiological contamination or render coffee palatable. Rather, Defendants argued that acrylamide levels in coffee cannot be reduced at all without negatively affecting safety and palatability.

75. While Plaintiff offered some evidence that consumption of coffee increases the risk of harm to the fetus, to infants, to children and to adults, Defendants' medical and epidemiology experts testified that they had no opinion on causation.

76. Although evidence showed that roasting coffee beans is necessary to make coffee palatable and roasting coffee beans reduces microbiological contamination in coffee, Defendants' proffered evidence that coffee itself confers some benefit to human health was not persuasive and was refuted by Plaintiffs' evidence.

77. Defendants did not establish that consumption of coffee confers a benefit to human health.

78. Defendants have failed to satisfy their burden of proving that sound considerations of public health support an alternate risk level for acrylamide in coffee.

79. To establish their ASRL defense, Defendants must prove an alternative risk level

for acrylamide in coffee by means of a scientifically valid quantitative risk assessment.

80. Defendants did not conduct a quantitative assessment of the risk of cancer from exposure to *acrylamide in coffee*.

81. Defendants did not present a quantitative risk assessment that quantitatively compared any alleged health benefits with any adverse effects of coffee consumption.

82. Assuming *arguendo* that the testimony of Darryl Sullivan and Dr. Scrafford, and the data of Covance Laboratories were all admissible in evidence and considered by the Court, Defendants nevertheless failed to meet their burden on the ASRL affirmative defense based on the credibility of witnesses and the weight of evidence being against Defendants.

83. Accordingly, the Court rules against Defendants and in favor of Plaintiff on Defendants' Alternative Significant Risk Level affirmative defense.

X. CONCLUSIONS

84. Defendants have the burden of proof to establish their Alternative Significant Risk Level affirmative defense by a preponderance of the evidence.

85. Defendants have failed to meet their burden of proof on their Alternative Significant Risk Level affirmative defense.

DATED: May 7, 2018

ELIHU M. BERLE

HONORABLE ELIHU M. BERLE
Superior Court of California
Los Angeles County

EXHIBIT “G”

SUPERIOR COURT OF CALIFORNIA, COUNTY OF LOS ANGELES

DATE: 02/16/18			DEPT. 323
HONORABLE ELIHU M. BERLE	JUDGE	R. ARRAIGA	DEPUTY CLERK
HONORABLE #5	JUDGE PRO TEM		ELECTRONIC RECORDING MONITOR
M. MOLINAR, C.A.	Deputy Sheriff	NONE	Reporter

1:30 pm	BC435759	Plaintiff Counsel	RAPHAEL METZGR	(X)
	COUNCIL FOR EDUCATION AND RESEA ON TOXICS	Defendant	JEFFREY MARGULIES	(X)
	VS	Counsel	JAMES M. SCHURZ	(X)
	STARBUCK CORP ET AL			
	***EXCEEDED C/W BC461182		*additional appearances	
	Complex 7/12/10 *LexisNexis*		are listed below*	

NATURE OF PROCEEDINGS:

APPLICATION OF PLAINTIFF TO FILE UNDER SEAL CONFIDENTIAL DECLARATION OF RAPHAEL METZGER REGARDING RELATIONSHIP BETWEEN GROCERY MANUFACTURERS' ASSOCIATION AND ITS MEMBERS, WITH CONFIDENTIAL DOCUMENTS ATTACHED AS EXHIBITS, IN SUPPORT OF PLAINTIFF'S REQUEST FOR JUDICIAL NOTICE OF COURT FILE & PLEADINGS IN DUKE II CASE

DEFENDANTS' JOINDER IN PLAINTIFF'S REQUEST TO FILE UNDER SEAL CONFIDENTIAL DECLARATION OF RAPHAEL METZGER REGARDING RELATIONSHIP BETWEEN GROCERY MANUFACTURERS' ASSOCIATION AND THE NATIONAL COFFEE ASSOCIATION AND ITS MEMBERS, WITH CONFIDENTIAL DOCUMENT ATTACHED AS EXHIBITS, IN SUPPORT OF PLAINTIFF'S REQUEST FOR JUDICIAL NOTICE OF COURT FILE & PLEADINGS IN DUKE II CASE;

The matters are called for hearing.

The parties argue the matters.

The Court does NOT find there exists the following:

1) An overriding interest that overcomes the right of public access to the record;

2) The overriding interest supports sealing the record;

3) A substantial probability exists that the

MINUTES ENTERED
02/16/18
COUNTY CLERK

SUPERIOR COURT OF CALIFORNIA, COUNTY OF LOS ANGELES

DATE: 02/16/18			DEPT. 323
HONORABLE ELIHU M. BERLE	JUDGE	R. ARRAIGA	DEPUTY CLERK
HONORABLE #5	JUDGE PRO TEM		ELECTRONIC RECORDING MONITOR
M. MOLINAR, C.A.	Deputy Sheriff	NONE	Reporter

1:30 pm	BC435759	Plaintiff Counsel	RAPHAEL METZGR	(X)
	COUNCIL FOR EDUCATION AND RESEA ON TOXICS	Defendant	JEFFREY MARGULIES	(X)
	VS	Counsel	JAMES M. SCHURZ	(X)
	STARBUCK CORP ET AL			
	***EXCEEDED C/W BC461182		*additional appearances	
	Complex 7/12/10 *LexisNexis*		are listed below*	

NATURE OF PROCEEDINGS:

overriding interest will be prejudiced if the record is not sealed;

4) The proposed sealing is narrowly tailored; and

5) No less restrictive means exist to achieve the overriding interest.

The above entitled matters are DENIED.

The Court orders the conditionally filed under seal document to be filed in open court this date.

The Unredacted Confidential Declaration Of Raphael Metzger Regarding Relationship Between Grocery Manufacturers' Association And The National Coffee Association And Its Members, With Confidential Documents Attached As Exhibits, In Support Of Plaintiff's Request For Judicial Notice Of Court File & Pleadings In Duke II Case is filed this date.

Plaintiff is directed to give notice and post copy of same on the parties' electronic service website.

ADDITONAL APPEARANCES VIA COURTCALL:

ROBIN STAFFORD	PHILIP A. LEIDER
ALECIA COTTON	LAUREN M. MICHALS
MEGAN IRWIN	RAOUL KENNEDY
BRENDAN W. BRANDT	

MINUTES ENTERED
02/16/18
COUNTY CLERK

METZGER LAW GROUP
A PROFESSIONAL LAW CORPORATION
RAPHAEL METZGER, ESQ., SBN 116020
KIMBERLY MILLER, ESQ., SBN 97738
ABRAHAM PARISER, ESQ., SBN 314524
401 E. OCEAN BLVD., SUITE 800
LONG BEACH, CA 90802-4966
TELEPHONE: (562) 437-4499
TELECOPIER: (562) 436-1561

Attorneys for Plaintiff,
Council for Education and
Research on Toxics ("CERT")

SUPERIOR COURT OF THE STATE OF CALIFORNIA

FOR THE COUNTY OF LOS ANGELES, CENTRAL CIVIL WEST

COUNCIL FOR EDUCATION AND RESEARCH ON TOXICS, a California corporation, acting as a private attorney general in the public interest;

Plaintiff,

vs.

STARBUCKS CORPORATION, a Washington corporation; et al.,

Defendants.

CASE NO. BC435759
Consolidated with Case No. BC461182
Assigned to the Honorable Elihu Berle, Dept. 323

UNREDACTED **CONFIDENTIAL DECLARATION OF RAPHAEL METZGER REGARDING RELATIONSHIP BETWEEN GROCERY MANUFACTURERS' ASSOCIATION AND THE NATIONAL COFFEE ASSOCIATION AND ITS MEMBERS, WITH CONFIDENTIAL DOCUMENTS ATTACHED AS EXHIBITS, IN SUPPORT OF PLAINTIFF'S REQUEST FOR JUDICIAL NOTICE OF COURT FILE & PLEADINGS IN *DUKE II* CASE**

LAW OFFICES OF
RAPHAEL METZGER
A PROFESSIONAL LAW CORPORATION
401 EAST OCEAN BOULEVARD, SUITE 800
LONG BEACH, CALIFORNIA 90802-4966

TELEPHONE (562) 437-4499
TOLL-FREE (877) TOX-TORT
TELECOPIER (562) 436-1561
WWW.TOXICTORTS.COM

PRACTICE CONCENTRATED IN TOXIC TORT & ENVIRONMENTAL LITIGATION
OCCUPATIONAL & ENVIRONMENTAL LUNG DISEASE, CANCER, AND TOXIC INJURIES

LAW OFFICES OF
RAPHAEL METZGER
A PROFESSIONAL LAW CORPORATION
401 EAST OCEAN BOULEVARD, SUITE 800
LONG BEACH, CALIFORNIA 90802-4966

TELEPHONE (562) 437-4499
TOLL-FREE (877) TOX-TORT
TELECOPIER (562) 436-1561
WWW.TOXICTORTS.COM

PRACTICE CONCENTRATED IN TOXIC TORT & ENVIRONMENTAL LITIGATION
OCCUPATIONAL & ENVIRONMENTAL LUNG DISEASE, CANCER, AND TOXIC INJURIES

DECLARATION OF RAPHAEL METZGER

I, Raphael Metzger, declare as follows:

1. I am an attorney at law, licensed and authorized to practice law in the State of California.

2. Unless the context indicates otherwise, I have personal knowledge of the matters set forth hereinafter and, if called as a witness, I would competently testify thereto.

3. My firm represents the Plaintiff, Council for Education and Research on Toxics ("CERT"), in these consolidated actions.

4. This Declaration is offered in support of Plaintiff's Request for Judicial Notice of the pleadings in *American Federation of Labor and Congress of Industrial Organizations, et al., v. George Deukmejian, Governor of the State of California, et al.* (Sacramento County Superior Court, Case No. 502541), and *AFL-CIO et al. v. Pete Wilson, et al.,* (Court of Appeal, Third Appellate District, Case No. C008697 (commonly known as the "*Duke II*" case).

5. The Grocery Manufacturers' Association (GMA) intervened in the case on behalf of its members (including members of the coffee industry), expressly alleging that "as a practical matter, the decision in this action will have a direct effect on GMA and its members.

6. The Defendants in this action are members and/or privies of members of the GMA. This is shown by various confidential documents that Defendants produced in this action.

7. Attached hereto as Exhibit "A" is a true and correct copy of a document produced by Kraft Foods titled "2005 Report to Contributors from Science Advisory Group, National Coffee Association of U.S.A., Inc." A section of this document titled "Acrylamide" states:

> The U.S. Food sector has chosen to coordinate its acrylamide activities on a general food basis (via GMA). In the specific case of a petition to then-governor of California about possible Proposition 65 consequences, the SAG contributing companies therefore signed as food companies and not as their coffee subsidiaries."

LAW OFFICES OF
RAPHAEL METZGER
A PROFESSIONAL LAW CORPORATION
401 EAST OCEAN BOULEVARD, SUITE 800
LONG BEACH, CALIFORNIA 90802-4966

TELEPHONE (562) 437-4499
TOLL-FREE (877) TOX-TORT
TELECOPIER (562) 436-1561
WWW.TOXICTORTS.COM

PRACTICE CONCENTRATED IN TOXIC TORT & ENVIRONMENTAL LITIGATION
OCCUPATIONAL & ENVIRONMENTAL LUNG DISEASE, CANCER, AND TOXIC INJURIES

8. Attached hereto as Exhibit "B" is a true and correct copy of a document produced by Smucker titled "Acrylamide Coalition Mitigation Project: Notes from 05-09-28 Conference Call." This document states that the purpose of the Acrylamide Coalition Mitigation Project is "to demonstrate to various audiences that the US food industry has been seriously addressing the presence of acrylamide in food by researching ways to mitigate its formation" and that the nature of the project is "to prepare a report of our efforts with a North American face." The report states that "the primary audiences are 1. FDA - to confirm our efforts, and to provide the agency substance to fend off moves to impose guidelines or levels in international regulatory forums, 2. California regulators and the public - to demonstrate our efforts and that . . . there is no quick fix . . . ." The document further states: "The project is a coalition project; GMA is serving as a coordinator to focus efforts to completion."

9. Attached hereto as Exhibit "C" is a true and correct copy of a document produced by Nestle titled "Progress and Development Guide: PDG 2010 - John Mwangi." This document describes a visit by Richard Stadler (Head of Quality Management of Nestle's Product Technology Center in Orbe, Switzerland) and John Mwangi (then Manager of Technical Regulatory Affairs of Nestle US) to the FDA. In this document Mr. Mwangi wrote: "Our Visit to the FDA was successful in influencing the FDA to use the tool box approach and against setting guidance values. Nega Beru at the FDA mentioned that FDA was going to issue a guidance document for the management of acrylamide which was not issued. We initially had offered to provide more data on Acrylamide to the FDA but on the advice of legal and of Nancy Rachman at GMA we were advised not to provide more data to the FDA because of the risk of the data being discovered in the event of a lawsuit under Prop. 65."

10. Attached hereto as Exhibit "D" is a true and correct copy of a document of the European Coffee Federation produced by Starbucks titled "NCA/SAG - ECF/Expert Group on Food Contaminants" dated May 9, 2012. Section 4 of this document is titled "FoodDrinkEurope Acrylamide Toolbox." This document states:

//

LAW OFFICES OF
RAPHAEL METZGER
A PROFESSIONAL LAW CORPORATION
401 EAST OCEAN BOULEVARD, SUITE 800
LONG BEACH, CALIFORNIA 90802-4966
TELEPHONE (562) 437-4499
TOLL-FREE (877) TOX-TORT
TELECOPIER (562) 436-1561
WWW.TOXICTORTS.COM

//

> The sectors provide the material for 'their' chapter in the FoodDrinkEurope Toolbox. ECF, being member of FoodDrinkEurope, is the source for the coffee chapter. The entire Toolbox is approved by the relevant FoodDrinnkEurope committee. As part of a revision process FoodDrinkEurope shares the revised Toolbox with the Groceries Manufacturers Association (GMA) of the USA for comments and endorsement....

11. Attached hereto as Exhibit "E" is a true and correct copy of an email chain produced by Nestle. The email chain includes an email from Richard Stadler to Ludovica Verzegnassi dated November 15, 2013 regarding the FDA's Draft Guidance on Acrylamide. In this email Dr. Stadler wrote: "I have read through this document and in my opinion Nestlé (NUSA) needs to provide comments either directly or via GMA." Ms. Verzegnassi responded to Dr. Stadler, copying Carolyn Meduski of Nestle USA Regulatory Affairs in Glendale, California: "I can coordinate with NUSA RSA to go through GMA."

I declare under penalty of perjury under the laws of the State of California that the foregoing is true and correct. Executed December 22, 2017, at Long Beach, California.

Raphael Metzger

PRACTICE CONCENTRATED IN TOXIC TORT & ENVIRONMENTAL LITIGATION : OCCUPATIONAL & ENVIRONMENTAL LUNG DISEASE, CANCER, AND TOXIC INJURIES

2005 REPORT TO CONTRIBUTORS

From

SCIENCE ADVISORY GROUP
NATIONAL COFFEE ASSOCIATION OF U.S.A., INC.

Eileen Madden, Ph.D.
SAG Chairperson

EXHIBIT A

Table of Contents

Report and Comments on 2004

Strategic Direction of SAG

At the end of 2000, the Science Advisory Group (SAG) developed a new strategic plan, which the NCA Board of Directors formally approved shortly thereafter. The agreed direction is for a more pro-active stance by the Group in promoting the beneficial aspects of coffee consumption.

2004 is the fourth year of the plan's implementation, and the main activities have been 1) co-founding the Vanderbilt Institute of Coffee Studies and continuing to monitor and evaluate the output of its studies; and 2) identifying and prioritizing research areas for potential positive effects of coffee consumption. SAG decided in 2003 to discontinue its funding to Vanderbilt-ICS, but its new strategic direction continues in all other respects.

This Annual Report updates you on the progress SAG has made on these activities as well as on areas that require further attention in pursuing SAG's strategic direction in 2005 and beyond.

Public Attention for Coffee and Health

Since adoption of the new strategic plan, considerable energy and coordination to propel SAG's direction and goals have been devoted by NCA in ongoing service to members and the industry. The topic of coffee and health has become a vital cornerstone of NCA's educational outreach to membership and the public, with dedicated programming at NCA conferences, stories in NCA publications, and messaging for public information.

Educational Offerings

In 2004, sessions on coffee and health were held at the NCA convention in March and at the Fall Educational Conference in October. In both sessions, a roundup of current research was presented to dispel old, negative myths and to detail the exploding body of evidence linking coffee with measurable disease-fighting properties.

Publications

The NCA's *Coffee Reporter* over the last year has carried numerous news stories on positive research findings regarding coffee and health, as well as covered and deflected breaking, potentially negative news. In fact, a frequently-appearing column devoted to the subject – *"Drink to Your Health"* -- was introduced in the publication in December 2003.

The *Coffee Reporter* coverage included such topics as:

- Diabetes: several articles on succession of four major studies, among others, confirming coffee's protective properties against development of Type II Diabetes
- Colon Cancer: German research confirming protective effect of compound unique to coffee, the strong antioxidant methylpyridinium

- Hydration – University of Nebraska Medical Center study finding caffeinated beverages as hydrating as water
- Athletic Performance – study published in *Current Sports Medicine Reports* concluding caffeine as an "ergogenic aid," improving endurance during prolonged exercise, boosting performance during short-term high-intensity athletics, enhancing concentration and reducing fatigue
- Rich source of antioxidants – study in *Journal of Agricultural and Food Chemistry* finding coffee has four times the antioxidants as green tea, and more than red wine, cocoa and herbal teas
- Coffee as a "Health Food" – roundup of positive scientific evidence and health

In addition, NCA staff was approached by a Toronto radio station to be a guest on an hour-long call-in program whose topic was "Coffee as Health Food." Most callers were noticeably eager to hear good news about coffee.

Category Promotion

Coffee and health also lies at the heart of the industry's first proactive foray in decades into category consumption promotion in the form of a new, multi-year, industry-supported public relations campaign, *Coffee Delivers*. From conceptualization, to message development, to execution of its creative elements, the campaign is dependent on, and unshakably faithful to, scientific inquiry sponsored and/or reviewed by SAG in pursuance of its new strategic direction.

The campaign was developed via independent NCA qualitative and quantitative market research concluding that consumers are eager to hear good news about coffee. The clearly winning messages, derived from focus groups and quantified through Internet surveys, were that coffee is good for one's physical health and for one's mental acuity and performance.

The parallel with SAG's strategic direction was immediately apparent to the Group and to the task force culled from the NCA Public Relations and Market Research committees that conducted the research. Moreover, the work of SAG in regularly monitoring and analyzing existing research on coffee and caffeine, as well as participating in scientific community dialogue and funding worthy studies, was directly aligned with what would need to be the foundation of the public relations campaign – the solid and rapidly growing body of scientific evidence that coffee is good for human health.

This confluence of the scientific literature and consumer attention makes the current climate ripe for promoting coffee and health among the American public. Going forward with developing and implementing such a public relations campaign, consequently, required the close collaboration and participation of SAG. The Group, in fact, has actively participated in meetings and regular correspondence with the NCA Public Relations Committee and the public relations counsel hired by NCA to execute the campaign. The NCA staff liaison to SAG also manages the work of the Public Relations and Market

Research committees, further facilitating ongoing, regular dialogue and coordination.

At the request of the Public Relations committee, in fact, SAG established a formal review and approval process for all campaign messages to ensure accuracy before release to the press and public. That process proved effective and efficient even under large-scale demands, as multiple presentations were reviewed prior to the campaign's kickoff event, a symposium for editors at the New York Academy of Sciences in October.

Promising new research recently completed and/or pending publication is being sought in order to provide additional, exclusive messages for the campaign. Working with SAG, the PR Committee and counsel regularly seek new sources in the scientific community for outreach and cooperation. This arrangement serves both the NCA, which can be first to go public with the findings and gain public relations advantage, as well as the researchers, who eagerly seek a vehicle for making their work known.

Coffee Science Source

As part of the *Coffee Delivers* campaign, the NCA's *Coffee Science Source* web site has been entirely revamped and relaunched. The new format invites visitors into the site's technical content with consumer-friendly articles on important health topics, linked to from inviting homepage graphics and text. On the revamped site is also an updated and expanded bibliography of abstracts and papers, which will be updated as appropriate with positive studies deemed noteworthy through SAG's ongoing literature review process.

Potential New Research

In line with the Group's new strategic direction, further efforts continue as in previous years as members continue to identify and prioritize research for additional, positive effects of coffee consumption. To that end, the Group has recommended allocating some of its carryover funds to two projects.

- Sponsorship of a half-day session on coffee/caffeine and cancer at the 30th Annual Winter Toxicology Forum Meeting in Washington, DC. The agenda will include a discussion of cancer epidemiology by Lynn Arab, visiting professor of epidemiology at UCLA, whose expertise is dietary factors in carcinogenesis. Also on the panel will be Dick Adamson (American Beverage Association), Jerry Rice (Georgetown), Lois Gold (UC, Berkeley), and Jim Coughlin. Dave Hatton of the FDA and Frances Smith of Consumer Alert will serve on the panel at the end of the sessions along with the speakers.
- A researcher previously from Vanderbilt is studying a link she discovered between an individual coffee compound and improved glucose uptake in the liver, which could prove to be the causal link between coffee and its demonstrated protective properties against the development of Type II Diabetes. It also explains the perceived connection between caffeine and glucose intolerance since the coffee compound appears to counteract the caffeine in the glucose

uptake system. SAG is considering sponsoring this research going forward.

In addition, coffee and its antioxidants remain one of the most interesting areas of discovery, and warrants wider attention. Good research on this subject has already been done in several centers in Europe and at Vanderbilt's' Institute for Coffee Studies. While a half-day workshop on the subject during an international coffee conference (ASIC 2003) was canceled, the scientific material on antioxidants in coffee is still available and should be used at a next opportunity.

In last year's report, SAG concluded that there is no need for funding of more studies in the very positive area of protective effects of coffee/caffeine on Parkinson's Disease. There is already ample scientific interest in this area and enough studies already ongoing that there is no need for extra SAG funding. In fact, the findings of a study recently published were publicized as part of the public relations campaign, and received considerable media attention as a result.

Co-operative Activities

Vanderbilt Institute of Coffee Studies

SAG co-funded Vanderbilt-ICS over a period of four years (1999 to 2002). In 2003, SAG discontinued this funding and recommended to its contributors that "if the Contributors are willing to spend a larger sum, SAG is willing to assist in selection of studies and coffee substances for testing in order to increase their relevance for actual coffee consumption." Instead, SAG recommends that its contributing companies channel their donations to ICS via SAG in order to optimize the value of the ICS work for the coffee sector. In the meantime, ICS is also seeking public funding through the National Institutes of Health.

International Colleagues

The major international counterparts to SAG are the Physiological Effects of Coffee (PEC) workgroup in Europe and AJCA in Japan. Both fund a substantial number of studies, mainly in the area of positive effects of coffee consumption, but also on topics that need clarification for defensive purposes. The projects are currently in the areas of mental performance, microcirculation, anti-carcinogenicity, liver protection, extensions on antioxidants, neurochemistry/Parkinson's, hyperactivity disorder, beneficial cardiovascular effects of coffee in smokers, preventive effects of specific coffee components on cancer, anti-obesity effects, suppression of hepatitis and other studies.

At its last meeting, SAG discussed additional coordination of efforts with colleagues in Europe, specifically PEC. Since SAG and PEC both monitor the scientific literature on coffee and caffeine, it was recommended that SAG should try to coordinate activities for effectiveness and cost efficiency. The SAG process is more advanced, with a system for regular monitoring and analysis of all literature through our outside consultant, whereas PEC reviews

the literature only when a member brings a paper to the group's attention, it was recommended that we approach PEC to jointly fund the existing SAG literature monitoring process.

Benchmarking of SAG Activity Level

SAG continues to do excellent work in monitoring the scientific literature, providing a critical firewall against findings that could impact negatively on the U.S. industry. However, its budget for funding new research, and therefore fulfilling its new strategic direction, remains significantly below the levels of its European counterparts and also its own historic levels.

The European coffee sector runs a comprehensive program to fund research that supports coffee consumption, funded via the Institute of Scientific Information on Coffee (ISIC) (functionally parallel to SAG's Board of Contributors). Total ISIC research funding currently runs at approximately US$ 300,000.

Historically, SAG funding ran significantly higher than current levels as well. In the early 1980s, it fluctuated between US$ 200,000 and US$ 500,000 per year, translating into a per-bag assessment for contributors of one-half to 5 cents per bag. In 2004, SAG contributors elected to fund SAG at the 2003 level, allowing for administrative costs to be covered and for the building of a reserve to undertake future research.

At this juncture, public sentiment and scientific evidence are dovetailing like never before toward a lasting positive impact on American consumer attitudes. At the same time, *Coffee Delivers* is already in place to provide the mechanism to parlay this historic confluence of substantive evidence and consumer receptivity into significant new opportunity for the U.S. coffee industry. Results in just the first few months of the campaign's scheduled three-year run have been nothing short of remarkable.

With the groundwork well established, the importance of SAG funding has never been more visible. Continued funding, at levels more historically and internationally proportionate, would be conducive to the underwriting of meaningful new research. Never before has this research carried such promise, delivering a welcome message to consumers already primed to embrace it.

Potentially Defensive Issues

Ochratoxin A

The main areas for defensive concern at this moment are the developments around Ochratoxin (OTA) in foods, particularly regarding regulatory developments in Europe on OTA in coffee. The EU has completed its regulatory process by passing legislation, effective January 1, 2005, that sets OTA limits of 5 ppb for roasted coffee and 10 ppb for soluble coffee. Previously, several individual European countries had already imposed regulatory limits on OTA in coffee, like Italy, Greece, Finland and Switzerland. Last December, Germany introduced very strict limits for OTA in coffee of 3

ppb for roasted coffee and 6 ppb for instant. It is known that the U.S. FDA has taken samples for OTA analysis. SAG continues to monitor FDA OTA surveillance; however, at this time, FDA risk assessments do not warrant regulatory action.

Acrylamide

Another issue of concern is acrylamide. The issue of acrylamide surfaced as a surprise to the entire food industry and international regulators when Swedish researchers reported in April 2002 about the presence of this carcinogenic component in a wide range of food items. Since then, much research about acrylamide has been done and is still ongoing in many centers around the globe. It is evident that acrylamide has been there since mankind started preparing foods by baking, frying and roasting. Acrylamide was shown to be carcinogenic in rodents, but direct evidence for human carcinogenicity is still lacking.

The U.S. food sector has chosen to coordinate its acrylamide activities on a general food basis (via GMA). In the specific case of a petition to then-governor of California about possible Proposition 65 consequences, the SAG contributing companies therefore signed as food companies and not as their coffee subsidiaries. The European authorities have taken more of a sector-by-sector approach. The European coffee sector recently communicated to governmental authorities that acrylamide formation occurs very early in the roasting process and is followed by very major reduction of the acrylamide level later in the roasting process.

Furan

Another item for potential defensive posturing is Furan. The FDA will hold a Food Advisory Committee meeting in June, 2005 specifically on the content of the substance in foods. The National Academy of Sciences put out a paper on acceptable exposure to Furan in spacecraft, and that number would be favorable if applied to foods. The National Food Processors Association is also currently working on the issue.

Caffeine

The food industry has expressed concern regarding the biased anti-caffeine work of Jack James prior to the publication of his work. The ILSI Caffeine Committee has discussed the matter, and they have conferred with CoSIC as well. The ILSI Committee has pulled together a summary of the literature for analysis and comment to short circuit potential lag time once James' work is published. SAG members agreed not to be drawn into a premature confrontation in the media with James before he publishes his work because it would only fuel the story.

Funding Issues

Due to budgetary concerns in 2003, SAG rejected funding of new research by Profession John Mann of Columbia University that sought to explore the reasons behind coffee consumption and lower rates of suicide and depression. However, this experience pointed up to the Group that large projects would cause similar budgetary concerns for the indefinite future in every instance funding is considered. Therefore, a solution was devised that would pave the way to making funding of future research less burdensome in any given year by building in additional surpluses over time, banking monies that could accumulate toward funding future research without a large outlay in any one year. To do this, NCA proposed keeping the per-bag assessment for contributions consistent from 2003 to 2004, and maintaining the same funding concept going forward, with potential increases to the per-bag assessments in subsequent years without specific proposals for research funding.

With this procedure in place and projecting available funds based on carryover funds banked through 2005, the Group has raised the possibility of funding research, already underway by Linda Shearer, Ph.D. formerly of Vanderbilt University's Institute of Coffee Studies and now of the University of Calgary on glucose uptake by the liver, preliminarily showing extraordinary, groundbreaking results. These preliminary results, in fact, may provide the missing link to the irrefutably positive findings in numerous studies about coffee's protective effect against the development of Type II Diabetes.

Given numerous positive findings on coffee/caffeine and cancer protection, versus old flawed research carrying negative implications, the Group perceived positive utility in sponsoring a formal literature review. After deciding an epidemiological review would be too costly, the Group elected the most cost-effective method for achieving their goal, namely sponsoring a review at an existing scientific forum. Therefore, the Group decided to fun a half-day session at the 30th Annual Winter Toxicology Forum Meeting in Washington, DC. On the agenda will be a discussion of cancer epidemiology with a distinguished panel including Lynn Arab (UCLA), Dick Adamson (American Beverage Association), Jerry Rice (Georgetown), Lois Gold (UC, Berkeley), and Jim Coughlin. Dave Hatton of the FDA and Frances Smith of Consumer Alert will moderate the sessions.

Funding Recommendation

It is recommended that SAG contributors, consistent with the funding concept adopted in 2004, fund SAG for the year 2005 at the same per-bag contribution paid by the respective contributors in 2004. Such action will allow SAG to undertake the modest research recommended and build reserve, funding a more aggressive approach to research in the future

Acrylamide Coalition Mitigation Project

Notes from 05-09-28 Conference Call

1. The participants discussed and reconfirmed the purpose and the nature of the project:
   a. To demonstrate to various audiences that the US food industry has been seriously addressing the presence of acrylamide in food by researching ways to mitigate its formation
   b. To prepare a report of our efforts with a North American face
      1. It's OK if we can simply change the spelling
      2. It's much better if we can provide detail that is clearly represents the situation in the US and Canada – local cultivars and their agronomic chemistry (e.g., white vs. yellow potatoes), growing and storage conditions, company and/or academic research conducted in the US or Canada, etc.
      3. Where projects or research were conducted on a trans-Atlantic basis we should identify it and be credited with our share, and also point out the industry's global approach to the problem.
      4. MN to contact Peter Ashby re shareable data from CIAA report.
   c. The primary audiences are
      1. FDA – to confirm our efforts, and to provide the agency substance to fend off moves to impose guidelines or levels in international regulatory forums
      2. California regulators and the public – to demonstrate our efforts and that this there is no quick fix
      3. The wider US public and opinion makers - to demonstrate our efforts and that this there is no quick fix
   d. The project is a coalition project; GMA is serving as a coordinator to focus efforts to completion
   e. The resulting report will be presented as a coalition document from the coalition association members; no brands or companies will be identified

2. The participants agreed that the four elements of the CIAA toolbox – agronomic, recipe, processing, final product characteristics - adequately covered the issues. It was felt that agronomic traits might have a large impact and could offer the biggest impact, and that finished product characteristics (e.g., color, storage) could be changed in only a limited way before an established product would no longer be acceptable, but that there could be more latitude when introducing new products.

3. The participants agreed that the identified sectors identified in the CIAA document needed to be included, particularly since these were identified in dietary exposure studies (FDA, JECFA) as the major contributors of acrylamide in the diet. Representatives from confectionery and almonds would also look into the availability of sector-specific information. Mark agreed to contact representatives of other sectors (e.g., prune juice, olives) to determine if they had something to contribute to the project.

4. For the food sectors, the participants agreed to the following:
   a. Potato products
      1. chips / snacks – P&G to provide most recent data; MN to contact Frito-Lay for same

EXHIBIT B

2. French Fries – McCain to revisit earlier work to determine what to include; ConAgra to do same and perhaps write entire chapter on agronomic, storage and finished product characteristics (Right, Jerry?)

b. Bread – ABA to contact its technical resources and AIB to identify shareable research.

c. Cookies and Crackers – Kraft, Kellogg/Keebler to identify existing pertinent data

d. Breakfast Cereals – Kellogg, General Mills, Post to dust off earlier project initiated with FPA in order to identify useful data.

e. Coffee – Kraft to contact PEC (or send PEC contact info to MN) re available data

f. Coffee Substitutes – No action at this time

g. Almonds – ABC to discuss their projects internally and determine availability of the data

h. Confectionery - Hershey to identify work done, possibly work with/through CMA.

i. MN to contact other sectors, e.g., prune juice, olives.

Progress and Development Guide

PDG 2010 - John Mwangi

Name: John Mwangi **Review Period:** 2010	**Current Position:** Manager, Technical Regulatory Affairs **Date of Last Review:** February 16, 2010

Achievements

Objectives	Results
1.0 Acrylamide 1.0 Plan a visit to the FDA along with Richard Stadler from PTC Orbe to present Nestle's mitigation strategies towards the reduction of acrylamide by End June. 1.1 Influence the FDA positions by providing data on Acrylamide developed at PTC Orbe to the Chemical Management Committee(CMC) of GMA towards a management system for acrylamide similar in approach to the CIAA toolbox and not towards the guidance values approach adapted by EFSA by End October 1.2 Prepare the business for FDA guidance on acrylamide by end July 1.3 Start a monitoring program for our products for acrylamide levels to get a baseline level for acrylamide by 4th quarter. **2 Prop 65** 2.0 Manage and advise the business of the impact of the chemicals that are currently proposed to be listed under Prop 65 BPA, Acrylamide, Methanol, 4 MEI. End July 2.1 Determine the impact of the safe habor level MADL/NSRL on our products and advise the business accordingly End JULY 2.2 Assesment of our products Mid September. **3.0 Improve impact of SRA website. (with Head of regualtory NCI to assure consistent approach is developed and implemented)** 3.1 Determine most effective distribution of documents/information between the NUSA and NCI intranet websites vs. Regulatory Team Rooms (s).e.g, more public vs. more department. 3.2 Determine from other function and internal customers the kind of information they would most like. Organize website and begin to populate accordingly.	**1.0 Acrylamide** **JMM Mid Year Comments** Richard Stadler and I made a sucessiful visit to the FDA on may 20th, 2010. We made a presentation on Nestle's efforts on the reduction of acrylamide that was very well received. We also had a length discussion about the management of the acylamide issue in Europe through setting of guidance values. we proposed to the FDA that we believe that the use of the CIAA tool box on acrylamide was the most practical approach for the US. 1.1 Our visit to the FDA was succesiful in influencing the FDA to use the tool box approach and against setting guidance values. Nega Beru at the FDA mentioned that FDA was going to issue a guidance document for the management of acrylamide which was not issued. We initially had offered to provide more data on Acrylamide to the FDA but on the advice of legal and of Nancy Rachman at GMA we were advised not to provide more data to the FDA because of the risk of the data being discovered in the event of a law suit under Prop 65. 1.2 The FDA guidance was not issued it was expected buy JULY. I prepared the busines to start monitoring for acrylamide as the expectation was the guidelines would be issued before the end of the year. **JMM final Year comments** 1.3 On the advice of legal. The business was asked not to begin testing before we had in place an attorney Client priviledge to protect the data from discovery under Prop 65. Once the attorney client priviledge was in place in the fourth queater. we started testing Panini's and Pizza, wafers, and cocoa liqour. This data is under attroney client priviledge **2.0 Prop 65** 2.0 Agreed to move the Prop 65 chemicals to the issue management sheets and keep track of them that way.

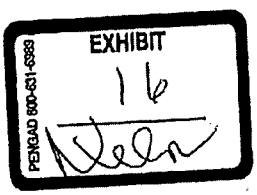

EXHIBIT C

3.3 Establish protocols

-to identify and distribute documents/information in the team rooms and application of Nestle Document Retention Policy.

-organize documents/information in the team rooms and application of the Nestle Document Retention Policy

3.4 Identify ways to increase traffic to the website and determine how to get feedback from visitors. Q409

4.0 Prepare Regulatory Affairs for Operations audits, as an auditable function and as a result to the plants and other functions

4.1 Identify and communicate names of Regulatory staff and resources available during plant audits.

4.2 Identify in the plant audit protocol the touch points regulatory is responsible for or contributes to for other functions, e.g, procedures activities, work products.

4.3 Assess readiness policies/procedures/practices for audits and adjust as needed the regulatory touch points in the audit as protocols and make sure we are ready for a full complaince audit

Added at Mid Year.

4.4 Complete the process descriptions for RSA by end of August

4.5 conduct an internal audit against our process end september 2010

Meet with Karen Young to learn from the NQMS regulatory audit in Canada. Incorporate those learnings into our audit protocol and audit Karen against the list of Guidance requirements.

Then Meet with Ed Trujillo and Miriam Maxwell first to educate them about the requirements. Then audit them against the GI requirements.

Meet with our new manager for Pizza educate them about the requirements and then audit against the GI requirements

2.1 The NSRL set for acrylamide as a carcinogen in California of 0.2 ug/day is so low that all our products will need a warning lable under Prop 65.

2.2 Data on acrylamide was not received until November due to the legal requirements. So assesment of our product will be done in the first quarter of 2011. We have to be careful how we handle the data because of the lawsuit.

3.0 Website:

JMM Mid Year comments

3.1. Developed and launched a new website, and a document management standard operation Procedure to set out which documents will go on the website and those that would end up on the Regulatory Share point team rooms.

3.2 Survey sent out August 13. Four respondents. on further discussion with Mark decided to organize the website and provide information that I believed is most current.

3.4 We have a Nutrition newsletter every time a new version is released we will send out an an email that would invite the recipients to visit the Regulatory website. On the website is a link with my email adresss to which visitors to the site can send comments.

4.0. Prepare regulatory Affairs for Operations audits as an auditable function and as a resource to the plants and other function.

This objective changed throughout the year. The initial goal was to identify the requirements as per the FSMS checklist. Which I did, then the respective GI requirements this was also done.

4.1 Names of the Managers were communicated to the plants.

4.2 Prepared a powerpoint presentation used for the Pizza and Vitality meeting in Chicago to identify all the Gi's that Regulatory is responsible for and all the other documents that are linked to the GI's.

JMM Final Year Comments

4.3 On the audit preparation we expect that the audit will be in July 2011. Todd Macnamara and Richard Hutson have been indentified as the Corporate offices functions champions (shared services). I have identified that the people Managers Ed Trujillo, Miriam Maxwell, Sandy Furbee, Elizabeth Jasek will be the lead auditors and expect the Internal audit training to be provide to them and I by February 2011. Then we will revise the Regulatory NQMS maps with input from the

Confectionery Division and the Beverage Divisions their processes have been phase 2 certified processes Early in February 2011. I will visit with Canadian office in February 18 to learn more from their processes and the benefits of implementation of their new process. Once the managers and I have received internal audit training we will use that training to identify gaps in our regulatory process map, Also concurrent with the auditing is the training in the content of the GI 90.003, 90.004, 90.005, 90.007, 90.010. Then from March-June we will be closing gaps identified by our internal audit We expect Phase 1 audit July 2011.

4.4 Revise the Regulatory process map based on input gathered from audits for the Confectionery and Beveage divisions. This work is ongoing so we will revise it again as we improve the processes.

4.5 Prepared and made a presentation on NQMS implementation at the Regulatory summit to prepare everyone for the implementation phase Oct 25. we have postponnerd the internal audit because we have yet to receive the training from OIT. I wil be attending the internal audit training Feb 15-17, 2011 only after that can we schedule an internal audit.

Met with Karen Young to incorporate learning of the NQMS audit into our preparation for the audit. I will be travelling to Toronto to meet with Karen and understand how their process differs with ours.

It has become eveident that we all the managers need internal audit training. I have organized that Ed, Sandy and I attend training this coming week in Carlsbad, California and Miriam and Liz attend training in Solon Mar 29- Apr 1, 2011. Only after that can we be in a position to conduct internal audit training.

Supervisor Comments October 15

John began this Performance Improvement Plan on April 1 and successfully completed it on September 30. After an initial slow start, John committed to improving his performance. He has demonstrated improvements in the Leadership Framework skills appropriate to his role as Manager, Technical Regulatory Affairs, and has taken a more active, results focused approach to his PDG objectives, in particular understanding the requirements for an NQMS audit.

I want to emphasize that John needs to maintain this level of performance and that in fact he will need to continue to elevate it to meet the demands of the business and the development of the role. Also, John can not expect his supervisor to provide the same level of attention and prodding as has been the case during the PIP; John needs to take responsibility and deliver this performance himself.

Leadership Framework

Opening Up

Strengths and Improvement Needs	Results
Know Yourself Knowing yourself is the ability to accurately identify and understand one's own strengths and improvement areas, understand their implications on one's effectiveness in the organization and take them into account to optimize performance.	
Insight Insight is the capacity to identify links between facts, ideas and situations that have no obvious connection with one another and to assemble them in a meaningful way. At a highly developed level, insight manifests itself as the creation of new ideas or the development of a long term vision.	
Service Orientation Service Orientation is the desire to help and serve one's customers in a way which best meets their actual needs. It is shown in the efforts a person will make to understand the customer's expectations and needs, to provide them with high quality service for a long-lasting and mutually profitable relationship. "Customer" can be any person or organization for whom the service is intended (internal client, colleagues at all levels, distributor, consumer etc...).	JMM Mid year comments 1.0 The Inventory of Customer information requirements project. Irina was the customer; Irina provided a deadline of August 16, which was met and kept her informed of the progress we are making. I got input from Mike Desso and Kevin Mathews. I was available to make sure that her deadline was met. The ice cream business was looking to make an all natural claim on the new Midas technology that was to be applied to the slow churned ice-cream Line. I had to get the ice cream business to comply with the Nestle standard on natural claims. The main consern was the addition of color to ice cream. The FDA is clear that when there has been an addition of color we cannot make a natural claim, but we can make a made with natural ingredients claim. **JMM final Year comments:** I received a request to make a presentation to help the new Nestle Pizza group integrate into the Nestle philosphy. I prepared a presentation on the relevant instructions from regulatory affairs. The Guidance Documents (GI

	90.003,90.004,90.005,90.007, 90.010, Nestle standard on Natural claims, nestle standard on fortification) and the relavant other associated instructions. Mark used the presentation to prepare his own comments to the group. I prepared and made a presentation at the Regulatory summit on the implementation on the Nestle Quality Management Sytsem (NQMS) and what the regulatory affairs group can expect from the implementation. NQMS implementation will continue into 2011 with a critical review of the regulatory affairs process map. internal audit training, Training in the GI's, auditing to identify the gaps. Then preparation for the final audit in July 2011.
Curiosity Curiosity means people are open minded to learn more about the environment, things and people, by asking probing questions, or doing ad hoc research to gain a better understanding of the context.	**JMM Mid year Comments** Mark requested that I develop a presentation to be made at the chicago Pizza and Vitality meeting on the relevant GI for regulatory affairs. I made a draft presentation which Mark used to develop his presentation to the Pizza and Viatlity meeting. **Jmm Final Year Comments** I found out through Nancy Rachman at the GMA Chemical Manangemnt Committee (CMC) That the Board of the PEW TRUST has sponsored a project on Food Additives. I recognized that this was going to be a threat to the safety of food additives. Due to the fact that the PEW TRUST is very influencial in washington DC. I informed Mark of the impending initiative. I requested to attend a GMA Meeeting where more information about this initiative was going to be presented. I attended the workshop orgainzed jointly by GMA and the PEW TRUST. This meeting confirmed my consern. I then issued an early warining to Vevey, informed Mark, Bruce and Olivier also Chris Pfeiffer in legal about the planed activities of the PEW TRUST. Also that their planned actvities will likely be media events and we need to be prepared for the media onslaught.
Courage Courage is linked to people's confidence in their capabilities and judgment. It allows them to take decisions, or make choices, at the same time evaluating the risks and being conscious of their responsibilities. Need to demonstrate more confidence in my abilities, knowledge and skills with the business partners and in project teams.	JMM Mid year coments The visit to the FDA is a good example of courage because the Company especialy QA wa reluctant for Nestle to have a meeting with the FDA. So reached out to Richard Stadler who is a recognized global expert on acrylamide and asked for a meeting with Dr Nega Beru head of the FDA contaminant group. Richard presented the work that Nestle has done in minizing acrylamide levels in food. Which gave the FDA confidence that we are the global leaders on this issue. Also we were able to influence the FDA against following the EU direction of using guidance values and persured them that use the toolbox approach.

	JMM Final year comments: GMA had just hired Dr Lean Brunner as the Chief Scientist the steering committee of the Chemical Management Committee (CMC) . As the steering group of the CMC we knew it was imperative that we quickly influence Dr Brunner. We asked for a meeting with Dr Brunner the objective to impress upon him the priorities of the CMC. We asked and were granted a meeting. I travelled to washington along with the other memebrs of the steering froup of the CMC, Henry (Coca-Cola), Craig (Kraft), Pat barone(Unilever), Steve hermansky (Conagra) and we had a initial very productive meeting . In which Dr Brunner challenged us to come up with a strategic plan for all the issues that we are working on. We have since held two follow up meetings. The strategic agenda of the CMC for 2011 is begging to take shape. Three key areas of work have emerged:1 the demonization of the food industry 2) Collaboration between the trade associations that represent the food industry GM/IFIC/ILSI 3) operational support that GMA provides it's members on recurring Food and chemical issues. The couragious initiative we took to reach out to Dr Brunner very early on is starting to pay dividend. The Funding of the Prop 65 issues will now come from a budget item as opposed to individual assesment of members as and when an issue arises. Also because of the early visit when the Pew Trust Issue arse Dr Brunner was able to champion it with the ESRAC committee.

Adding Value

Strengths and Improvement Needs	Results
Result Focus The drive to meet or exceed ambitious performance objectives and quality standards, deliver business results and continually find sustainable improvements to methods and processes. Persist in overcoming obstacles. Identify opportunities and try to do things differently in order to significantly improve efficiency, quality productivity, or client satisfaction.	**JMM Mid Year comments:** As manager responsible for the ice-cream business I was agressively recruiting for the position of a regulatory specialist to support the ice cream business. This proved challenging because the business required that the psoition be located in Bakersfield. All the suitable candidates who were interetsed in the psoition were not willing to reloctae to Bakersfled. I got word that Ed Trujillo who previously held the position was interested in coming back. He had both the ice-cream background and had a home in Bakersfield. We interviewed Ed for the specialist position and he turned out to be better qualified for a managers position. He is now back with us as manager for Ice cream, Beverage and Confections. **JMM Year End comments.** Huito Blue color. I have taking the initiative to follow up with legal to determine the best way to seek an opinion from the FDA. Chris Pfeiffer and I met with Fred Dagnan

	external counsel and he advised that we need to inform WILD that we will be seeking an opinon with the FDA and ask them to come along or if not that we will go alone. I have reached out to the project coordinator to find out who is the legal Contact in WILD so that Chris pfeiffer can talk to them about approaching the agency. On the child labor issue. I am following up with Luise Hilsen to determine what needs to be done to meet the ILO requirementss. **JMM Year End Comments** ILSI hired a summer post doctorate student to write a paper on a acrylamide.The original draft contained data that would have played into in to the hands of the anti acrylamide lawyers. I reviewed the paper and then shared my comments with Richard Stadler and then relayed the Nestle comments to the ILSI Food safety committee and we were able to correct the irroneous impression created by the data.
Initiative Initiative makes people act in a proactive way by taking action and not simply thinking about the future. People with initiative not only react to situations but also anticipate future opportunities or problems, and act upon them well in advance. Not wait for all the data/all the answers before acting to seize a present opportunity. Analyze past suceesses for how things were accomplished and apply them to current opportunities.	**JMM mid Year comments:** We have been anticipating that the FDA will be implementing a monitoring system for acrylamide. So reached out to Richard Stadler at PTC Orbe and I requested for a meeting with the FDA. As a way to build our networks with the FDA contaminant group and also to share with the FDA data that Nestle has gathered in minimizing acrylamide and to illustrate the challenges we face reducing the level of acrylamide in many categories of food such as coffee. The visit was sucessiful in helping us to understand the FDA's approach to the managing of acrylamide in food. The FDA staff asked many questions about various approaches that we have used. One approach has been used un Europe the setting of guidance values for each category of food and the other is using the Tool Box approach similar to the CIAA tool box .Richard and I made pursuasive arguments against the setting of guidance values because they are difficult to manage. Also the levels of acrylamide especially in wheat varieties vary with seasons. The CIAA toolbox approach where the FDA and the industry regularily update the site on the latest methhods and tools for the reduction is what we prefer and hope the FDA will adopt. We believ they took our advise since they did not release any guidance to the contrary **JMM Year End Comments:** The pesticide issue at Freehold: Freehold has been importing raw tea from (China, Thailand, mexico, Switzerland, Chile, Colombia, Philipines, Malaysia,South Korea, venezuela, Brazil, Canada, Vietnam, New Zealand, that use pesticides that do not

	have a maximum pesticide Residue (MRL's) set in US and also exporting the tea powder to countries that do not have tolerances set for some of the pesticide residues. I worked closely with Tim jackson and Jim Barden QA manager at Freehold to research and I find out the approved list of pesticide MRL's set in each of the 15 countries we export the tea powder to in order for us to understand in which countries we are compliant and which countries we are not compliant. I also suggested that we use the Codex list, but we still found pesticides that are not on the codex list list such as Carbendazim.
Innovation & Renovation People exhibiting this behavior challenge the status quo in a drive for improvement, and come up with new ideas to operate more efficiently. At a highly developed level, they act as change catalysts for the whole organization.	

Dealing with Others

Strengths and Improvement Needs	Results
Proactive Cooperation Proactive cooperation implies working collaboratively with others, demonstrating commitment to achieve group objectives, understanding the needs and goals of others and adapting own views and behavior when appropriate. It may involve the sacrifice of individual objectives, with a view to achieving group objective. Actively contribute ideas, energy, and bring a desire to suceed as a team maintaining others motivation in the face of adversity.	**JMM Mid year comments:** I Worked collaboratively with Todd Macnamara and Cynthia Rodriquez in Quality assuarnce to solve a pesticide issue in which we were finding residues of carbendazim in Grape juice.Carbendazim does not have a set tolerance in the US and therefore is illegal. On further investigation we found out that it was a breakdown product of thiophanate methyl an approved pesticide. We carried out investigations using spray records from the juice supplier to be certain the supplier was not applying carbendazim it was a breakdown product. **Jmm Final review comments:** Worked collaboratively with Karen Magill on the NQMS map for regulatory affairs. to learn the basis for the selection of the processes and the reference documents and the KPI's.
Impact/Convince Others Convincing others, either directly or using appropriate third parties, in order to get their commitment to ideas, projects or actions that are in the Company's interest. Take the presentation advantage course when offered in Glendale. With Director identify opportunities to practice	**JMM Mid year Comments:** On Acylamide there was a lot of consern in the Company about making a trip to the FDA to make a presentation on progress Nestle has made on reducing levels of Acrylamide in foods. I held a number of conversations with Bruce Kohnz and with Mark and with Paul Casaletto and Rick Jarman in Nestle Nutrition to convince everyone that since Netsle had generated most of the data on acrylamide that the FDA would appreciate learning that and that we would not divulge any data that would be damaging to us rather we would be perceived as being proactive and the visit would open the door to our undrstanding of the FDA's thinking

	on acrylamide. The visit did infact give us a better understanding of the FDA's position and in our exchange with Dr Nega Beru and Henry Kim we were able to convince the FDA that managing acrylamide through setting guidance levels was going to be very difucit and that the more prudent approach is by using the CIAA acrylamide tool box. This did turnout to be the FDA's preffered approach. **JMM Final Review Comments:** For the Regulatory Affairs summit. I prepared a presentation that explained in detail the steps we were going to take to implement the Nestle NQMS. The tools at our disposal. Since he presentation I have had request for more information form Sandra Furbee and her group to explian further the requirements of NQMS and have agreed to set up a series of interwise session to go over the preseentation that Mark and made to the Pizza group in Chicago and also the presentation that i prepared showing the Gi's for regulatory and the related documents.

Inspiring People

Strengths and Improvement Needs	Results
Lead People Leading people is the ability to unite individuals, make them believe in themselves and in what they are doing, so they push their limits and are encouraged to outperform. It implies actively demonstrating the behaviors that are consistent with Nestlé Management and Leadership Principles.	
Develop People Developing people means helping individuals identify their short and long-term development needs, encouraging their individual learning by providing them with appropriate support.	
Practice What You Preach Practice what you preach means acting consistently with and embodying the Nestlé Principles and Values, including "Walking the talk" even when it is difficult to do so.	

Knowledge

Strengths and Improvement Needs	Results
Product Knowledge	
Professional Knowledge & Skills	

Nature of the Contribution

Transforms

- In her/his position brings major changes.
- Is widely recognized for her/his vision and ideas.
- Has a strong influence on the organization.
- Displays initiative. Knows how and when to take risks, demonstrates great creativity to get things moving.
- As a leader her/his creativity and initiative mark her/him as someone who initiates major changes.

- Her/his performance significantly exceeds expected results, even when dealing with complex assignments.

Steers
- Has full control of her/his role and responsibilities.
- Generally exceeds her/his position's objectives and accountabilities.
- Is a recognized expert in her/his fields of competence.
- Her/his performance ususally exceeds expected results.
- Is self-reliant and requires minimum supervision.

Masters
- Fulfills her/his role and establishes her/his credibility in the work environment.
- Her/his performance matches expectations, she/he reaches expected results.
- Sets priorities, is self-reliant in managing her/his position.

Acquires
- Begins to fulfill her/his role but still needs to develop in certain job requirements.
- Is establishing her/his credibility in the work environment.
- Requires close supervision and support together with frequent feed-back.
- If the person has occupied the position for over 2 year, she/he must either improve her/his performance or seek a new position.

Trails
- Her/his performance is significantly lower than expected.
- Maintaining this level of performance is not deemed acceptable. Decisions must be taken to remedy the situation.

New
- He/she is new to the company or recently promoted/transferred into a new/different position; Too soon to assess his/her performance in the new role.

Career & Development Plan

Immediate (current review period)

Action Plan	Results
1. Developing people for high performance- Completed 5/4/2010 2. Impact and convince others - Seek feedback from Chris Pfeiffer. Met with Chris Pfeiffer over lunch her suggestion is to demonstrate more confidence in my presentation . Had lunch withTodd Macnamara to get input on how I can better improve my message. Todd Macnamara 04/26/10- suggested, practice being comfortable speaking infront of people, rejoin toastmasters need to know the material and have a presentation you know well. Plan to tell a story. 3. Register for the Presentation advantage course as soon as dates for Glendale are posted. 4. Registered for Decision making and problem solving with six hats thinking 8/12/2010	Completed Decision making and problem solving with six hats thinking 8/12/2010 Registered in Presentation advantage April 12, 2011 offered in Glendale California.

Long-term (2 to 4 years)

Action Plan	Results
1 Continue to develop in the current position.	

Comments

Manager's Comments

Progress and Development Guid

Employee's Comments

Approval & Acknowledgements

Manager approval of final review
Employee acknowledgement of final review

European Coffee Federation

NCA/SAG – ECF/Expert Group on Food Contaminants
Wednesday 09 May 2012
Brussels

Present:

ECF Expert Group on Food Contaminants:
Helmut Günther
Steven Biesterveld
Gloria Pellegrino
Marino Petracco
Oliver Süße-Hermann
Roel Vaessen

SAG:
Norm Ouellette
Dan Steffen

Morrison Foerster (by telephone):
Michèle Corash
Robin Stafford

1. Opening, approval of the agenda and antitrust statement

This meeting between NCA/SAG and ECF/Expert Group on Food Contaminants aimed to ensure consistency of approach and messaging by the North American and European coffee sectors and to collaborate in a pre-competitive setting on research activities so as to prevent duplication of effort. The agenda was approved; the antitrust statement was duly noted.

2. Update Proposition 65 developments related to acrylamide

Mr. Ouellette provided an update of the Proposition 65 process. One of the key issues is whether acrylamide is a by-product of process necessary for palatability. Plaintiff takes the view that palatable coffee can be produced with none or less acrylamide. Plaintiff suggested that three companies are working on mitigation options one of them being Novozymes. The other two are possibly enzyme supplier DSM and Zeracryl (lactic acid bacteria).

The US Food and Drug Administration (FDA) is tracking the issue; Health Canada can be expected to model its policy on the developments in the EU.

3. Update on EU monitoring related to acrylamide in food and expectations for legislative activities

At the moment the EU regulatory system consists of:
- Monitoring of the presence of acrylamide in foodstuffs by national food safety authorities under guidance of the European Commission.

EXHIBIT D

- Commission Recommendation C(2010) 9681 final of 10 January 2011. This sets indicative values which may trigger investigative action by national food safety authorities. Reference is made to the FoodDrinkEurope Toolbox to determine adequate measures by food business operators.
- Additionally food safety authorities can check for adherence to the ALARA (as low as reasonably achievable) principle, regardless whether the indicative values are exceeded.

The current situation for the European coffee sector is contradictory: on the one hand the indicative values are rarely – if at all - exceeded, on the other hand the overall levels remain largely unchanged. Even though authorities recognise that there are currently no workable mitigation options available for coffee, the inability to reduce levels will not be politically acceptable in the longer term and pressure to find and apply mitigation options will increase. Because of the history of 'signal values' in Germany, there is strong insistence from retail on coffee suppliers to abide by the latest signal value of 280 mg/kg for roasted coffee.
When looking at the outcome of the EU acrylamide monitoring programme, it should be recognised that the age of the coffee is not recorded or compensated for. In- or decreases of averages may therefore be caused by older or fresher samples.

4. FoodDrinkEurope Acrylamide Toolbox

The sectors provide the material for 'their' chapter in the FoodDrinkEurope Toolbox. ECF, being member of FoodDrinkEurope, is the source for the coffee chapter. The entire Toolbox is approved by the relevant FoodDrinkEurope committee. As part of a revision process FoodDrinkEurope shares the revised Toolbox with the Groceries Manufacturers Association (GMA) of the USA for comments and endorsement. It is also presented to the European Commission for comments with a view to continue inclusion on the DG SANCO (Directorate General Health and Consumer Affairs) website. FDA may be aware, but is not a formal partner in the process.

It was noted that even sectors where asparagines is being applied successfully had not made any commercial statements on this. That would run counter to the generally accepted principle in the food industry that food safety is not a competitive topic.

5. Outcome of previous research activities with Novozymes

Trials in 2008/2009 indicated that applying asparaginase enzymes in coffee is not a tool to reduce AA levels at this stage. Reasons:
- Low efficiency (10-45%)
- Negative influence on quality
- Concerns if a viable, safe and sustainable commercial plant process is possible and practical.

6. Planned research activities (internal and with Novozymes)

Since the 2008/2009 trials further work has been done on asparaginase application. An very informative update was provided in presentations by Novozymes and CR3-Hermsen to the ECF Technical & Regulatory Committee and the German Coffee Association on 14 December 2011. However, because of the proprietary nature of the commercial scale enzyme application process developed by CR3-Hermsen, it was not possible to replicate the results or to make the process conditions generally available. Therefore ECF is in an advanced stage of setting up lab-scale trials with Novozymes for a combination of steam treatment and enzyme application. Novozymes will be responsible for the green coffee treatment and ECF for the roasting. ECF to check that steaming is done with realistic parameters. Roasting details are to be determined. Options: roast colour, heat input or loss of mass. A limited sensory assessment on expert level is foreseen to ascertain that the flavour impact is essentially as expected from the steaming process and that the enzyme application itself has no appreciable impact. It is important to recognise that lab-scale steaming will differ from industrial scale.

The SAG representatives indicated that for the US situation a full sensory assessment is highly relevant. This should preferably be done by a specialised external company. After a further exchange the meeting agreed to propose to Novozymes a revised set of trials with a larger volume and additional variations to allow for full sensory assessment:

Green coffee: Vietnam Robusta

1. untreated green reference
2. soaking only, no enzyme (process reference to (4)
3. Steaming plus soaking, no enzyme (process reference to (5)
4. Soaking only, with enzyme
5. Steaming plus soaking, with enzyme

Roasting: 3 roast conditions to cover light, medium and dark roasts

Roasted samples to be shipped to the USA for sensory assessment. Acrylamide analysis to be done at Eurofins for consistency of analysis with all other trials. Limited chemical check with caffeine as indicator. Extensive chemical analysis not opportune at this stage, but frozen samples may be kept for future use. If the protocol works a next series of trials can be set up for Arabica coffee.

Next steps:

- SAG to indicate volume needed for sensory assessment
- ECF to prepare revised proposal for Novozymes
- SAG and ECF to develop timeline and costs. SAG is willing to co-fund.

The meeting had a brief exchange on the trials to test the hypothesis of other pathways. Current knowledge indicates a very limited impact. Outcome expected in Q3.

Future line of communication will be between Messrs. Ouellette and Vaessen. Mr. Ouelette to ensure communication with SAG/NCA and Mr. Vaessen with Expert Group/ECF. ECF to communicate with Novozymes with copy to Mr. Ouellette.

7. Position of other enzyme suppliers

On 10 May a first exploratory meeting will take place with enzyme supplier DSM, who has now indicated an interest to collaborate with the coffee sector through ECF. Clearly ECF cannot give exclusivity to one enzyme supplier if there are more interested parties. DSM has also been in touch with NCA. The outcome of the meeting on 10 May will be shared.

8. Review of alternative mitigation options

Several suggestions have been made, but none are promising for coffee. Acrylamide is reduced during storage, but this cannot be considered as a mitigation option since it reduces remaining shelf-life and negatively effects quality.

In Canada asparaginase is approved for some foods, but not specifically for coffee. Enzyme suppliers have not yet requested approval.

9. Collaboration ECF – NCA/SAG

See item 6.

10. Next meeting

The next ECF Expert Group on Contaminants meeting will take place on the 6th of June. The next SAG meeting will be on 22 August. A joint meeting (most likely by teleconference) is tentatively foreseen in early December.

-o-o-o-

Rijswijk, 14 May 2012

From: Nelson,Mark,GLENDALE,Regulatory & Scientific Affairs
Sent: Friday, November 15, 2013 12:09 PM
To: Carvalho,Erika,MARYSVILLE,PTC Marysville NCE Coordination
Cc: Meduski,Carolyn,GLENDALE,NUSA T&M Glendale Regulatory Affairs
Subject: RE: Draft Guidance on Acrylamide

Erika –

Perhaps things have changed this week, but I thought we were still responsible for regulatory in the US.

In future, would you reach out to us before getting the whole world involved, or at least include us when you do. ☺

I'm interested in what Richard thinks should be comment on.

Mark

From: Meduski,Carolyn,GLENDALE,NUSA T&M Glendale Regulatory Affairs
Sent: Friday, November 15, 2013 8:58 AM
To: Nelson,Mark,GLENDALE,Regulatory & Scientific Affairs
Subject: FW: Draft Guidance on Acrylamide

Reading through this string of emails just realized that when the project CLAR becomes functional that there is additional Nestle regulatory stakeholders to consider – those in the PTCs. Erika Carvalho started circulating through her network and somehow got to Ludo, which she sent to head of QA.

Richard feels comments are needed.

From: Verzegnassi,Ludovica,VEVEY,CT-RSA
Sent: Friday, November 15, 2013 2:57 AM
To: Stadler,Richard,VEVEY,NQAC
Cc: Meduski,Carolyn,GLENDALE,NUSA T&M Glendale Regulatory Affairs
Subject: RE: Draft Guidance on Acrylamide

I can coordinate with NUSA RSA to go through GMA.
Let me know when you want to work on the doc

From: Stadler,Richard,VEVEY,NQAC
Sent: vendredi 15 novembre 2013 09:54
To: Verzegnassi,Ludovica,VEVEY,CT-RSA
Subject: RE: Draft Guidance on Acrylamide

Hi Ludo
I have read through this document and in my opinion Nestlé (NUSA) needs to provide comments either directly or via GMA. I suggest that together we draft first comments and share these with the US colleagues, collating all input at latest by beginning December.
Would you co-ordinate this activity with the relevant RSA colleagues ? perhaps easier and more efficient.
Best wishes
Richard

EXHIBIT E

From: Verzegnassi,Ludovica,VEVEY,CT-RSA
Sent: vendredi 15 novembre 2013 09:15
To: Huggett,Anthony,VEVEY,CO-QM
Cc: Stadler,Richard,VEVEY,NQAC
Subject: FW: Draft Guidance on Acrylamide

FYI, in case Richard had not forwarded it yet
Regards
Ludovica

D. Other foods

Coffee. Coffee is a significant source of acrylamide exposure for adults. Limited information is available on factors known to affect acrylamide concentrations in coffee.

[13] The Maillard reaction is a non-enzymatic reaction between sugars and proteins that occurs upon heating and that produces browning of some foods. See http://www.merriam-webster.com/dictionary/maillard%20reaction.
[14] For purposes of this guidance, the term "rework dough" refers to dough that is left over from preparing dough for manufacturing (such as trimmings left from cutting cookies on a baking sheet) and then is fed into the manufacturing process again.

Robusta beans have somewhat higher acrylamide levels than arabica beans.. Dark roast coffee has less acrylamide than light roast coffee (since acrylamide formed early in roasting is destroyed later in the roasting process). Acrylamide levels in roasted coffee decline during long-term storage. Also, different preparation methods (e.g., espresso versus filter brewed) result in different levels of acrylamide in coffee as consumed (Refs. 15, 27-28, 109).

A number of mitigation methods have been suggested for coffee, such as steam roasting and asparaginase treatment (Refs. 15, 110), but FDA is not aware of any proven mitigation measures. In more recent laboratory and pilot trials, treatment of green coffee beans with asparaginase resulted in lower acrylamide levels (10-45 percent) after roasting compared with untreated roasted beans, but coffee taste was significantly and negatively affected (Ref. 27). A viable commercial process is not yet available (Ref. 27).

From: Raederer,Marc,MARYSVILLE,PTC Marysville
Sent: jeudi 14 novembre 2013 21:43
To: Labrunie,Thierry,ORBE,Compliance
Cc: Heeb,Thomas,MARYSVILLE,PTC
Subject: FW: Draft Guidance on Acrylamide
Importance: High

Fya – common approch would be better

From: Carvalho,Erika,MARYSVILLE,PTC Marysville NCE Coordination
Sent: Thursday, November 14, 2013 1:32 PM
To: Anantharaman-Barr,Gillian,MARYSVILLE,PTC Marysville RTD Beverages; Cotter,Sean,MARYSVILLE,RTD Technology; Dyer,Randy,MARYSVILLE,NCE; Gallo,James,MARYSVILLE,Management Services; Gibson,William,MARYSVILLE,Coffee; Jolly,Mary,MARYSVILLE,RTD Products; Leas,Alain,MARYSVILLE,Portfolio Management; Lepior,Robert,MARYSVILLE,Knowledge to Consumer Links; McCarty,Allison,MARYSVILLE,Direction; Moulin,Cedric,MARYSVILLE,PTC Marysville Packaging; Nickle,Lawrence,MARYSVILLE,Quality; Paine,Jennifer,MARYSVILLE,Nestlé Professional; Raederer,Marc,MARYSVILLE,PTC Marysville; Rousset,Philippe,MARYSVILLE,PTC Marysville RTD Beverages; Yunker,Kenneth,MARYSVILLE,Engineering
Subject: FDA: Draft Guidance on Acrylamide
Importance: High

Der all,

FDA has just published a DRAFT guidance on how to reduce acrylamide for cereal, coffee and potato based foods. **The Draft is still for comments during next 60 days.**

Let me know if you would like to organize PTCM comments and we can discuss to join efforts and align with other stakeholders , such as PTC Orbe, NUSA and CTRSA.

Please distribute the documentation amongst your team or to whom you believe proper.

Thank you,

Erika Carvalho
Regulatory Affairs Manager / NCE Coordination
Nestle Product Technology Center
809 Collins Ave., Marysville, OH - USA 43040
Phone: +1 (937) 645-2395
Fax: +1 (937) 644-0509
erika.carvalho@rd.nestle.com
Visit us at PTC Marysville

From: U.S. Food & Drug Administration (FDA) [mailto:fda@service.govdelivery.com]
Sent: Thursday, November 14, 2013 9:21 AM
To: Carvalho,Erika,MARYSVILLE,PTC Marysville NCE Coordination
Subject: CFSAN Constituent Update

Center for Food Safety and Applied Nutrition - Constituent Update

Constituent Updates are also available on the web at
http://www.fda.gov/Food/NewsEvents/ConstituentUpdates/default.htm

FDA Issues Draft Guidance for Industry on How to Reduce Acrylamide in Certain Foods

November 14, 2013

The U.S. Food and Drug Administration (FDA) has issued draft guidance for the food industry to help growers, manufacturers and food service operators take steps to reduce levels of acrylamide in certain foods.

Efforts to reduce acrylamide levels are already underway in many sectors throughout the food industry. In issuing its draft guidance, the FDA seeks to support industry sectors that have taken a wait-and-see approach, and to help all companies – particularly smaller ones with fewer resources – reduce acrylamide in products susceptible to its formation.

Acrylamide is a chemical that can form in some foods during certain types of high-temperature cooking, such as frying, roasting and baking. Acrylamide in food is a concern because the National Toxicology Program (an interagency program that evaluates possible health risks associated with exposure to certain chemicals) characterizes the substance as "reasonably anticipated to be a human carcinogen."

To help mitigate potential human health risks, the FDA's draft guidance recommends that companies be aware of the levels of acrylamide in the foods they produce and consider adopting approaches, if feasible, that reduce acrylamide in their products. The draft guidance also offers a range of possible approaches that growers, manufacturers and food service operators can take to help reduce acrylamide levels.

The draft guidance, which is non-binding, covers raw materials, processing practices, and ingredients affecting potato-based foods (such as french fries and potato chips), cereal-based foods (such as cookies, crackers, breakfast cereals and toasted bread) and coffee, each of which is a significant source of acrylamide exposure.

The draft guidance is part of a number of activities initiated by the FDA to study acrylamide in food and help manage potential risks to human health. For example, the FDA is planning to publish additional data on acrylamide levels in certain foods based on its recent data collection and analysis. A summary of the FDA's acrylamide work is available in a Q&A on the agency's website.

Because acrylamide is found primarily in potato-based foods, cereal-based foods, and coffee, for consumers, the FD 's best advice to help limit one's acrylamide intake is to adopt a healthy eating plan, consistent with the Dietary Guidelines for Americans, that:

- Emphasizes fruits, vegetables, whole grains, and fat-free or low-fat milk and milk products;
- Includes lean meats, poultry, fish, beans, eggs, and nuts; and
- Is low in saturated fats, *trans* fats, cholesterol, salt (sodium) and added sugars.

Additional advice to consumers pertaining to acrylamide, including recommended food storage and preparation methods, is available on FDA.gov.